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(54) Title: SUPPRESSORS OF CYTOKINE SIGNALING; RELATED REAGENTS			
(57) Abstract Purified genes encoding intracellular regulatory molecules from a human, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding these molecules are provided. Methods of using said reagents and diagnostic kits are also provided.			

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SUPPRESSORS OF CYTOKINE SIGNALING: RELATED REAGENTS

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This filing is a PCT Application claiming priority to provisional U.S. Patent Applications USSN 60/055,804, filed August 15, 1997, and USSN 60/053,153, filed July 18, 1997. Also incorporated by reference are provisional U.S. Patent Applications USSN 60/055,853, filed August 15, 1997, and USSN 60/053,244, filed July 18, 1997.

FIELD OF THE INVENTION

The present invention pertains to compositions related to proteins which function, e.g., in suppressing intracellular signaling pathways, e.g., cytokine signaling. In particular, it provides purified genes, proteins, antibodies, and related reagents useful, e.g., to regulate growth hormone-like or cytokine-regulated intracellular processes, including transcription or genes in various cell types, including immune cells.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to the technique of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner

- workings of this network. While it remains clear that much of the response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now
- 5 generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play a critical role in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell
- 10 modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders. Some of these factors are hematopoietic growth factors, e.g., granulocyte colony stimulating
- 15 factor (G-CSF), and others are regulatory molecules. See, e.g., Thomson (1994; ed.) The Cytokine Handbook (2d ed.) Academic Press, San Diego; Metcalf and Nicola (1995) The Hematopoietic Colony Stimulating Factors Cambridge University Press; and Aggarwal and Gutterman (1991) Human
- 20 Cytokines Blackwell Pub.

- Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and differentiation of, e.g., pluripotential hematopoietic stem cells into vast numbers
- 25 of progenitors comprising diverse cellular lineages making up a complex immune system. Proper and balanced interactions between cellular components are necessary for a healthy developmental or immune response. The different cellular lineages often respond in a different
- 30 manner when lymphokines are administered in conjunction with other agents.

- In the immune system, many of the effects of known cytokines on gene transcription are known to be mediated by cytokine inducible DNA binding proteins. See, e.g.,
- 35 Paul (ed. 1994) Fundamental Immunology, 3rd ed., Raven Press, New York, NY. The mechanisms of signal transduction have been an area of active recent study, and involve protein phosphorylation and dephosphorylation with, e.g., the Janus kinases (JAKs) and Signal

Transducers and Activators of Transcription (Stats). See, e.g., Ihle (1996) Cell 84:331-334; ;Ivashkiv (1995) Immunity 3:1-4; and Ihle and Kerr (1995) Trends in Genetics 11:69-74.

- 5 The lack of knowledge regarding the mechanisms of signaling involved in the regulation of cell cycle or transcriptional elements has hampered the ability of medical science to specifically regulate cell division or cellular responses, including immune responses. The
10 present invention provides compositions which will be important in such regulation.

SUMMARY OF THE INVENTION

- The present invention is based in part upon the
15 discovery of intracellular regulatory molecules which can block signal transduction, e.g., through growth factor- or cytokine-receptor superfamily signaling mechanisms. These proteins exhibit a structural feature designated a SOCS box. See Hilton, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:114-119. Moreover, the SOCS3 protein can
20 block the IL-2 induced signaling via the STAT5, establishing function of the SOCS proteins as suppressors of cytokine signaling.

- The invention provides a substantially pure or
25 recombinant SOCS14 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 2 or 6; a natural sequence SOCS14 of SEQ ID NO: 2 or 6; a fusion protein comprising SOCS14 sequence; a substantially pure or recombinant SOCS15 (also designated
30 WDS11) protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 4 or 8; a natural sequence SOCS15 (WDS11) of SEQ ID NO: 4 or 8; a fusion protein comprising SOCS15 (WDS11) sequence; a substantially pure or recombinant SOCS17
35 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 10; a natural sequence SOCS17 of SEQ ID NO: 10; a fusion protein comprising SOCS17 sequence; a substantially pure or recombinant SOCS18 protein or peptide exhibiting identity
40 over a length of at least about 12 amino acids to SEQ ID

NO: 12; a natural sequence SOCS18 of SEQ ID NO: 12; a fusion protein comprising SOCS18 sequence; a substantially pure or recombinant SOCS19 protein or peptide exhibiting identity over a length of at least
5 about 12 amino acids to SEQ ID NO: 14; a natural sequence SOCS19 of SEQ ID NO: 14; a fusion protein comprising SOCS19 sequence; or a substantially pure or recombinant WDS12 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 16;
10 a natural sequence WDS12 of SEQ ID NO: 16; or a fusion protein comprising WDS12 sequence. In preferred embodiments, the portion is at least about 25 amino acids. In other embodiments, the: SOCS14 comprises a mature sequence of SEQ ID NO: 2 or 6; SOCS15 (WDS11)
15 comprises a mature sequence of SEQ ID NO: 4 or 8; SOCS17 comprises a mature sequence of SEQ ID NO: 10; SOCS18 comprises a mature sequence of SEQ ID NO: 12; SOCS19 comprises a mature sequence of SEQ ID NO: 14; WDS12 comprises a mature sequence of SEQ ID NO: 16; protein or
20 peptide: is from a warm blooded animal selected from a mammal, including a primate; comprises at least one polypeptide segment of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of SOCS14, SOCS15
25 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a mammalian SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits identity over a length of at least about 20
30 amino acids to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits at least two non-overlapping epitopes which are specific for a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits identity over a length of at least about 25 amino acids to a primate
35 SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a
40 natural sequence. Various preferred embodiments include

a composition comprising: a sterile SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein or peptide; the SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration. The invention further provides a fusion protein, comprising: mature protein comprising sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another SOCS or WDS protein.

These reagents also make available a kit comprising such a protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Providing an antigen, the invention further provides a binding compound comprising an antigen binding portion from an antibody, which specifically binds to a natural SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide comprising sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; is raised against a mature SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is raised to a purified SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is immunoselected; is a polyclonal antibody; binds to a denatured SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits a K_d to antigen of at least 30 μM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. Preferred kits include those containing the binding compound, and: a compartment comprising the binding compound; and/or instructions for use or disposal of reagents in the kit. Many of the kits

will be used for making a qualitative or quantitative analysis.

Other preferred compositions will be those comprising: a sterile binding compound, or the binding
5 compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

- The present invention further provides an isolated
10 or recombinant nucleic acid encoding a protein or peptide or fusion protein described above, wherein: the SOCS or WDS family protein is from a mammal, including a primate; or the nucleic acid: encodes an antigenic peptide sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16;
15 encodes a plurality of antigenic peptide sequences of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; exhibits identity to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label;
20 comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the SOCS or WDS family protein; or is a PCR
25 primer, PCR product, or mutagenesis primer. In certain embodiments, the invention provides a cell or tissue comprising such a recombinant nucleic acid. Preferred cells include: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian
30 cell; a mouse cell; a primate cell; or a human cell.

- Other kit embodiments include a kit comprising the described nucleic acid, and: a compartment comprising the nucleic acid; a compartment further comprising a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein
35 or polypeptide; and/or instructions for use or disposal of reagents in the kit. In many versions, the kit is capable of making a qualitative or quantitative analysis.

- Other nucleic acid embodiments include those which: hybridize under wash conditions of 50° C and less than
40 500 mM salt to SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15;

exhibits identity over a stretch of at least about 30 nucleotides to a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12. In other embodiments: the wash conditions are at 55° C and/or 300 mM salt; 60° C and/or 150 mM salt; the identity is over a stretch is at least 55 or 75 nucleotides.

In other embodiments, the invention provides a method of modulating physiology or development of a cell or tissue culture cells comprising introducing into such cell an agonist or antagonist of a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 I. General

It is to be understood that this invention is not limited to the particular compositions, methods, and techniques described herein, as such compositions, methods, and techniques may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which is only limited by the appended claims.

As used herein, including the appended claims, singular forms of words such as "a," "an," and "the" include their corresponding plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to "a polynucleotide" includes one or more different polynucleotides, reference to "a composition" includes one or more of such compositions, and reference to "a method" include reference to equivalent steps and methods known to a person of ordinary skill in the art, and so forth.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are

described below. All publications, patent applications, patents, and other references discussed above are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate any such disclosure by virtue of its prior invention. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety including all figures, references, and drawings.

The proliferation, differentiation, and physiological responses of many cell lineages are regulated by secreted proteins, e.g., cytokines. These molecules often exert their biological effects through binding to cell surface receptors that are associated with one or more members of the Janus Kinase (Jak) family of cytoplasmic tyrosine kinases. For example, cytokine induced receptor dimerization leads to the activation of JAKs, rapid tyrosine phosphorylation of cytoplasmic domains, and subsequent recruitment of various signaling proteins to the receptor complex, including members of the STAT family of transcription factors. The JAK and STAT proteins are enzymes which act to transduce a signal from the cell surface to the nucleus, thereby serving as the pathway to signal the cell to respond physiologically to an external signal. These pathways have been shown to involve certain protein phosphorylation or dephosphorylation steps, thereby leading to response or lack of response by the cell. See, e.g., Ihle (1996) Cell 84:331-334; Ivashkiv (1995) Immunity 3:1-4; Ihle, et al. (1995) Ann. Rev. Immunol. 13:369-398; Ihle and Kerr (1995) Trends in Genetics 11:69-74; and Darnell, et al. (1994) Science 264:1415-1421.

A number of novel genes have been identified from mouse or humans which appear to inhibit STAT function. See, e.g., Yoshimura, et al. (1995) EMBO J. 14:2816-2826; Matsumoto, et al. (1997) Blood 89:3148-3154; Starr, et al. (1997) Nature 387:917-921; Endo, et al. (1997) Nature 387:921-924; and Naka, et al. Nature 387:924-929. The

present invention provides additional genes with sequence related to those, designated Suppressors Of Cytokine Signaling or WDS: SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12.

5 A primate, e.g., human, SOCS14 cDNA fragment and corresponding open reading frame are provided in (SEQ ID NO: 1 and 2). The translation exhibits significant matching and similarity to other identified SOCS family members. The internal stop codon indicates some errors in the sequence at
10 or near those positions. Additional refined sequence of primate, e.g., human, SOCS14 is provided in SEQ ID NO: 5 and 6.

15 A rodent, e.g., mouse, SOCS15 cDNA fragment and corresponding open reading frame are provided in SEQ ID NO: 3 and 4. The translation exhibits significant matching and similarity to other identified SOCS family members. The internal stop codon indicates some errors in the sequence at or near those positions.

20 A rodent, e.g., murine SOCS17 CDNA and corresponding open reading frame are provided in SEQ ID NO: 9 and 10. Nucleotide may be A, C, T, or G at positions: 1680, 1691, 1696, 1704, 1707, 1728, 1740, 1743, 1746, 1755, 1760, 1770, 1773, 1802, 1816, 1817, 1823, 1826, 1827, 1846, 1851, 1857, 1861, 1880, 1885, 1909, 1917, 1920, 1929,
25 1946, 1953, 1967, 1968, 1980, 1991, 1995, 2001, 2004, 2021, 2033, 2034, 2035, 2036, 2037, 2039, 2040, 2042, 2048, 2051, 2054, 2061, 2075, 2081, 2083, 2084, 2085, 2088, 2105, 2121, 2124, 2132, 2137, 2147, 2149, 2151, 2152, 2160, 2165, 2177, 2179 and 2196; nucleotide may be
30 A or C at position 494; nucleotide may be C or T at positions: 498, 501, 1455, 1524, 1527, 1621, 1829, and 2072; nucleotide may be G or C at positions: 499, 1618, and 1664; nucleotide may be G or T at position 1673; and nucleotide may be A, C, or G at positions: 1819, 1840,
35 and 2089 (see SEQ ID NO: 26).

 A primate, e.g., human, SOCS18 nucleotide and corresponding amino acid sequence are provided in SEQ ID NO: 11 and 12. Nucleotide may be A or C at positions: 740, 797, 2139, and 2184; nucleotide may be G or T at
40 positions: 761, 1313, 1508, and 2226; nucleotide may be C

or T at positions 746, 1460, 1499, 2009, 2010, 2199, and 2225; nucleotide may be A or G at positions 788, 863, 1550, 2178, 2188, 2197, and 2211; nucleotide may be G or C at positions: 1163, and 1544; nucleotide may be A or T at positions 2058, and 2128; and nucleotide may be A, C, T, or G at position 2251 (see SEQ ID NO: 27).

A primate, e.g., human, SOCS19 nucleotide and corresponding amino acid sequence are provided in SEQ ID NO: 13 and 14. Nucleotide may be A, C, T, or G at positions: 2078, and 2116; and nucleotide may be G or C at position 2063 (see SEQ ID NO: 28).

Finally, a primate, e.g., human, WDS12 nucleotide and corresponding amino acid sequence is provided in SEQ ID NO: 15 and 16. Nucleotide may be A, C, T, or G at positions: 108, and 109; nucleotide may be A or G at positions: 236, 238, and 1258; nucleotide may be G or T at position 233; nucleotide may be G or C at position 234; nucleotide may be C or T at position 237; and nucleotide may be A or T at position 239 (see SEQ ID NO: 29).

SOCS proteins are a family of proteins ranging from approximately 30-60 Kd which inhibit JAK kinase activity. The amino portion of SOCS proteins contain an SH2 binding motif and the carboxy portion of the molecule contains a SOCS box motif which may play a role in dimerization of SOCS proteins. The WDS are closely related in sequence.

SOCS3 expression is induced by IL-2 and can be detected by approximately 1 hour after IL-2 activation. Subsequently, SOCS expression is decreased relatively rapidly (e.g., approximately 8 hrs after activation). Western blots show that SOCS3 interacts with IL-2 receptor and JAK1 following IL-2 stimulation.

II. Definitions

The term "binding composition" refers to molecules that bind with specificity to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, e.g., in an antibody-antigen interaction. However, other compounds, e.g., binding proteins, may also specifically associate

with SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 proteins in contrast to other molecules.

Typically, the association will be in a natural

physiologically relevant protein-protein interaction,

5 either covalent or non-covalent, and may include members of a multiprotein complex, including carrier compounds or dimerization partners. The molecule may be a polymer, or chemical reagent. A functional analog may be a protein with structural modifications, or may be a wholly

10 unrelated molecule, e.g., which has a molecular shape which interacts with the appropriate protein binding

determinants. The proteins may serve as agonists or

antagonists of the binding partner, see, e.g., Goodman,

et al. (eds.) (1990) Goodman & Gilman's: The

15 Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press, Tarrytown, N.Y.

The term "binding agent: SOCS or :WDS protein complex", as used herein, refers to a complex of a

binding agent and a SOCS14, SOCS15 (WDS11), SOCS17,

20 SOCS18, SOCS19, or WDS12 protein that is formed by

specific binding of the binding agent to the respective

SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein. Specific binding of the binding agent means

that the binding agent has a specific binding site that

25 recognizes a site on the SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein. For example,

antibodies raised to a SOCS14, SOCS15 (WDS11), SOCS17,

SOCS18, SOCS19, or WDS12 protein and recognizing an epitope on the SOCS or WDS protein are capable of forming

30 a binding agent: SOCS or :WDS protein complex by specific binding. Typically, the formation of a binding agent:

SOCS or :WDS protein complex allows the measurement of SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein in a mixture of other proteins and biologics.

35 The term "antibody: SOCS or :WDS protein complex" refers to an embodiment in which the binding agent, e.g., is an antibody. The antibody may be monoclonal, polyclonal, or a binding fragment of an antibody, e.g., an Fv, Fab, or

F(ab)2 fragment. The antibody will preferably be a

40 polyclonal antibody for cross-reactivity purposes.

"Homologous" nucleic acid sequences, when compared, exhibit significant similarity, or identity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison and/or phylogenetic relationship, or based upon hybridization conditions. Hybridization conditions are described in greater detail below.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, cDNA, genomic DNA, or a mixed polymer, which is substantially separated from other biologic components which naturally accompany a native sequence, e.g., proteins and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs, or analogs biologically synthesized by heterologous systems. Further, the term includes double-stranded or single-stranded embodiments. Where single-stranded, the nucleic acid may be either the "sense" or the "antisense" strand. A substantially pure molecule includes isolated forms of the molecule. An isolated nucleic acid will usually contain homogeneous nucleic acid molecules, but will, in some embodiments, contain nucleic acids with minor sequence heterogeneity. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

As used herein, the terms "SOCS" or "WDS" protein shall encompass, when used in a protein context, a protein having amino acid sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 or a significant fragment of such a protein, preferably a natural embodiment. The term "protein" or "polypeptide" is meant any chain of amino acids, regardless of length or postranslation modification (e.g., glycosylation or phosphorylation). Further, the term encompasses polypeptides which are pre- or pro-proteins. The invention also embraces a polypeptide which exhibits similar structure to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, e.g., which interacts with SOCS or WDS protein specific

binding components. These binding components, e.g., antibodies, typically bind to a SOCS or WDS protein, respectively, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM.

The term "polypeptide" or "protein" as used herein includes a significant fragment or segment of a SOCS or WDS protein, and encompasses a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids, e.g., 35, 40, 45, 50, 60, 70, 80, etc. The invention encompasses proteins comprising a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12. Features of one of the different genes should not be taken to limit those of another of the genes.

A "recombinant" nucleic acid is defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants. Thus, for example, products made by transforming cells with any non-naturally occurring

vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode polypeptides similar to fragments of these antigens, and fusions of sequences from various different species variants.

"Solubility" is reflected by sedimentation measured in Svedberg units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation velocity was classically performed in an analytical ultracentrifuge, but is typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d ed.) W.H. Freeman & Co., San Francisco, CA; and Cantor and Schimmel (1980) Biophysical Chemistry parts 1-3, W.H. Freeman & Co., San Francisco, CA. As a crude determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less than about 3S. Solubility of a polypeptide or fragment

depends upon the environment and the polypeptide. Many parameters affect polypeptide solubility, including temperature, electrolyte environment, size and molecular characteristics of the polypeptide, and nature of the solvent. Typically, the temperature at which the polypeptide is used ranges from about 4° C to about 65° C. Usually the temperature at use is greater than about 18° C and more usually greater than about 22° C. For diagnostic purposes, the temperature will usually be about room temperature or warmer, but less than the denaturation temperature of components in the assay. For therapeutic purposes, the temperature will usually be body temperature, typically about 37° C for humans, though under certain situations the temperature may be raised or lowered in situ or in vitro.

The size and structure of the polypeptide should generally be in a substantially stable state, and usually not in a denatured state. The polypeptide may be associated with other polypeptides in a quaternary structure, e.g., to confer solubility, or associated with lipids or detergents in a manner which approximates natural lipid bilayer interactions.

The solvent will usually be a biologically compatible buffer, of a type used for preservation of biological activities, and will usually approximate a physiological solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, a detergent will be added, typically a mild non-denaturing one, e.g., CHS (cholesteryl hemisuccinate) or CHAPS (3-[3-cholamidopropyl)-dimethylammonio]-1-propane sulfonate), or a low enough concentration as to avoid significant disruption of structural or physiological properties of the protein.

"Substantially pure" in a protein context typically means that the protein is isolated from other contaminating proteins, nucleic acids, and other biologicals derived from the original source organism. Purity, or "isolation" may be assayed by standard methods, and will ordinarily be at least about 50% pure,

more ordinarily at least about 60% pure, generally at least about 70% pure, more generally at least about 80% pure, often at least about 85% pure, more often at least about 90% pure, preferably at least about 95% pure, more
5 preferably at least about 98% pure, and in most preferred embodiments, at least 99% pure. Similar concepts apply, e.g., to antibodies or nucleic acids.

"Substantial similarity" in the nucleic acid sequence comparison context means either that the
10 segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least 56%, more generally at least 59%, ordinarily at least 62%, more
15 ordinarily at least 65%, often at least 68%, more often at least 71%, typically at least 74%, more typically at least 77%, usually at least 80%, more usually at least about 85%, preferably at least about 90%, more preferably at least about 95 to 98% or more, and in particular
20 embodiments, as high as about 99% or more of the nucleotides. Alternatively, substantial similarity exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence derived from SEQ ID NO: 1, 3,
25 5, 7, 9, 11, 13, or 15. Typically, selective hybridization will occur when there is at least about 55% similarity over a stretch of at least about 30 nucleotides, preferably at least about 65% over a stretch of at least about 25 nucleotides, more preferably at
30 least about 75%, and most preferably at least about 90% over about 20 nucleotides. See Kanehisa (1984) Nuc. Acids Res. 12:203-213. The length of similarity comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at
35 least about 17 nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to
40 100 or more nucleotides, e.g., 150, 200, etc.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequent coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., supra).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by

- a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.
- Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul, et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Nat'l Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

"Stringent conditions", in referring to homology or substantial similarity in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. The combination of parameters is more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370.

A nucleic acid probe which binds to a target nucleic acid under stringent conditions is specific for said target nucleic acid. Hybridization under stringent conditions should give a background of at least 2-fold over background, preferably at least 3-5 or more. Such a probe is typically more than 11 nucleotides in length,

and is sufficiently identical or complementary to a target nucleic acid over the region specified by the sequence of the probe to bind the target under stringent hybridization conditions.

- 5 SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein from other mammalian species can be cloned and isolated by cross-species hybridization of closely related species. See, e.g., below. Similarity may be relatively low between distantly related species, and
10 thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody preparation which exhibits less species specificity may be useful in expression cloning approaches.

- The phrase "specifically binds to an antibody" or
15 "specifically immunoreactive with", when referring to a protein or peptide, refers to a binding reaction which is determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biological components. Thus, under designated
20 immunoassay conditions, the specified antibodies bind to a particular protein and do not significantly bind other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity for a particular
25 protein. For example, antibodies raised to the protein immunogen with the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 can be selected to obtain antibodies specifically immunoreactive with SOCS or WDS proteins and not with other proteins. These
30 antibodies recognize proteins highly similar to the homologous SOCS or WDS protein.

III. Nucleic Acids

- Primate or rodent SOCS or WDS protein is each
35 exemplary of a larger class of structurally and functionally related proteins. These soluble proteins will serve to transmit signals between different cell types. The preferred embodiments, as disclosed, will be useful in standard procedures to isolate genes from
40 different individuals or other species, e.g., warm

blooded animals, such as birds and mammals. Cross hybridization will allow isolation of related genes encoding proteins from individuals, strains, or species. A number of different approaches are available to

5 successfully isolate a suitable nucleic acid clone based upon the information provided herein. Southern blot hybridization studies can qualitatively determine the presence of homologous genes in human, monkey, rat, mouse, dog, cow, and rabbit genomes under specific

10 hybridization conditions.

Complementary sequences will also be used as probes or primers. Based upon identification of the likely amino terminus, other peptides should be particularly useful, e.g., coupled with anchored vector or poly-A

15 complementary PCR techniques or with complementary DNA of other peptides.

Techniques for nucleic acid manipulation of genes encoding SOCS or WDS proteins, such as subcloning nucleic acid sequences encoding polypeptides into expression

20 vectors, labeling probes, DNA hybridization, and the like are described generally in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2nd ed.) Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, which is incorporated herein by reference.

25 This manual is hereinafter referred to as "Sambrook, et al."

There are various methods of isolating DNA sequences encoding SOCS or WDS proteins. For example, DNA is isolated from a genomic or cDNA library using labeled

30 oligonucleotide probes having sequences identical or complementary to the sequences disclosed herein. Full-length probes may be used, or oligonucleotide probes may be generated by comparison of the sequences disclosed. Such probes can be used directly in hybridization assays

35 to isolate DNA encoding SOCS or WDS proteins, or probes can be designed for use in amplification techniques such as PCR, for the isolation of DNA encoding SOCS or WDS proteins.

To prepare a cDNA library, mRNA is isolated from

40 cells which expresses a SOCS or WDS protein. cDNA is

prepared from the mRNA and ligated into a recombinant vector. The vector is transfected into a recombinant host for propagation, screening, and cloning. Methods for making and screening cDNA libraries are well known.

- 5 See Gubler and Hoffman (1983) Gene 25:263-269 and Sambrook, et al.

For a genomic library, the DNA can be extracted from tissue and either mechanically sheared or enzymatically digested to yield fragments of about 12-20 kb. The
10 fragments are then separated by gradient centrifugation and cloned in bacteriophage lambda vectors. These vectors and phage are packaged in vitro, as described in Sambrook, et al. Recombinant phage are analyzed by plaque hybridization as described in Benton and Davis
15 (1977) Science 196:180-182. Colony hybridization is carried out as generally described in e.g., Grunstein, et al. (1975) Proc. Natl. Acad. Sci. USA, 72:3961-3965.

DNA encoding a SOCS14 or SOCS15 protein can be identified in either cDNA or genomic libraries by its
20 ability to hybridize with the nucleic acid probes described herein, e.g., in colony or plaque hybridization assays. The corresponding DNA regions are isolated by standard methods familiar to those of skill in the art. See, e.g., Sambrook, et al.

25 Various methods of amplifying target sequences, such as the polymerase chain reaction, can also be used to prepare DNA encoding SOCS or WDS proteins. Polymerase chain reaction (PCR) technology is used to amplify such nucleic acid sequences directly from mRNA, from cDNA, and
30 from genomic libraries or cDNA libraries. The isolated sequences encoding SOCS or WDS proteins may also be used as templates for PCR amplification.

Typically, in PCR techniques, oligonucleotide primers complementary to two 5' regions in the DNA region
35 to be amplified are synthesized. The polymerase chain reaction is then carried out using the two primers. See Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA. Primers can be selected to amplify the entire regions
40 encoding a full-length SOCS or WDS protein or to amplify

smaller DNA segments as desired. Once such regions are PCR-amplified, they can be sequenced and oligonucleotide probes can be prepared from sequence obtained using standard techniques. These probes can then be used to isolate DNA's encoding SOCS or WDS proteins.

Oligonucleotides for use as probes are usually chemically synthesized according to the solid phase phosphoramidite triester method first described by Beaucage and Carruthers (1983) Tetrahedron Lett. 22(20):1859-1862, or using an automated synthesizer, as described in Needham-VanDevanter, et al. (1984) Nucleic Acids Res. 12:6159-6168. Purification of oligonucleotides is performed e.g., by native acrylamide gel electrophoresis or by anion-exchange HPLC as described in Pearson and Regnier (1983) J. Chrom. 255:137-149. The sequence of the synthetic oligonucleotide can be verified using, e.g., the chemical degradation method of Maxam, A.M. and Gilbert, W. in Grossman, L. and Moldave (eds.) (1980) Methods in Enzymology 65:499-560 Academic Press, New York.

Isolated nucleic acids encoding SOCS or WDS proteins were identified. The nucleotide sequences and corresponding open reading frames are provided in SEQ ID NO: 1 through 16.

These SOCS or WDS proteins exhibit limited similarity to portions other intracellular proteins. In particular, β -sheet and α -helix residues can be determined using, e.g., RASMOL program, see Sayle and Milner-White (1995) TIBS 20:374-376; or Gronenberg, et al. (1991) Protein Engineering 4:263-269; and other structural features are defined in Lodi, et al. (1994) Science 263:1762-1767.

This invention provides isolated DNA or fragments to encode a SOCS or WDS protein. In addition, this invention provides isolated or recombinant DNA which encodes a protein or polypeptide which is capable of hybridizing under appropriate conditions, e.g., high stringency, with the DNA sequences described herein. Said biologically active protein or polypeptide can be an intact protein, or fragment, and have an amino acid

sequence as disclosed in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16, particularly natural embodiments. Preferred embodiments will be full length natural sequences. Further, this invention contemplates the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to a SOCS or WDS protein or which were isolated using cDNA encoding a SOCS or WDS protein as a probe. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others. Also embraced are methods for making expression vectors with these sequences, or for making, e.g., expressing and purifying, protein products.

A DNA which codes for a SOCS or WDS protein will be particularly useful to identify genes, mRNA, and cDNA species which code for related or similar proteins, as well as DNAs which code for homologous proteins from different species. There are likely homologs in other species, including primates, rodents, canines, felines, and birds. Various SOCS or WDS proteins should be homologous and are encompassed herein. However, even proteins that have a more distant evolutionary relationship to the antigen can readily be isolated under appropriate conditions using these sequences if they are sufficiently homologous. Primate SOCS or WDS proteins are of particular interest.

Recombinant clones derived from the genomic sequences, e.g., containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and organisms, and for gene therapy. See, e.g., Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199.

IV. Antibodies

Antibodies can be raised to various SOCS14 or SOCS15 proteins, including individual, polymorphic, allelic, strain, or species variants, and fragments thereof, both in their naturally occurring (full-length) forms and in their recombinant forms. Additionally, antibodies can be raised to SOCS or WDS proteins in either their active forms or in their inactive forms. Anti-idiotypic antibodies may also be used.

10 A. Antibody Production

A number of immunogens may be used to produce antibodies specifically reactive with SOCS or WDS proteins. Recombinant protein is the preferred immunogen for the production of monoclonal or polyclonal antibodies. Naturally occurring protein may also be used either in pure or impure form. Synthetic peptides, made using the human SOCS14 or SOCS15 protein sequences described herein, may also be used as an immunogen for the production of antibodies to SOCS14 or SOCS15 proteins. Recombinant protein can be expressed in eukaryotic or prokaryotic cells as described herein, and purified as described. Naturally folded or denatured material can be used, as appropriate, for producing antibodies. Either monoclonal or polyclonal antibodies may be generated for subsequent use in immunoassays to measure the protein.

Methods of producing polyclonal antibodies are known to those of skill in the art. Typically, an immunogen, preferably a purified protein, is mixed with an adjuvant and animals are immunized with the mixture. The animal's immune response to the immunogen preparation is monitored by taking test bleeds and determining the titer of reactivity to the SOCS or WDS protein of interest. When appropriately high titers of antibody to the immunogen are obtained, usually after repeated immunizations, blood is collected from the animal and antisera are prepared. Further fractionation of the antisera to enrich for antibodies reactive to the protein can be done if desired. See, e.g., Harlow and Lane; or Coligan.

Monoclonal antibodies may be obtained by various techniques familiar to those skilled in the art.

Typically, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell (see, Kohler and Milstein (1976) Eur. J. Immunol. 6:511-519, incorporated herein by reference).

- 5 Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired
- 10 specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode
- 15 a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells according, e.g., to the general protocol outlined by Huse, et al. (1989) Science 246:1275-1281.

- Antibodies, including binding fragments and single
- 20 chain versions, against predetermined fragments of SOCS or WDS protein can be raised by immunization of animals with conjugates of the fragments with carrier proteins as described above. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies
- 25 can be screened for binding to normal or defective SOCS or WDS proteins, or screened for agonistic or antagonistic activity, e.g., effect on cell cycle progression or transcription of specific genes. These monoclonal antibodies will usually bind with at least a
- 30 K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 10 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

- In some instances, it is desirable to prepare
- 35 monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.) Lange Medical Publications,
- 40 Los Altos, CA, and references cited therein; Harlow and

- Lane (1988) Antibodies: A Laboratory Manual CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York, NY; and particularly in Kohler and Milstein (1975) Nature 256:495-497, which discusses one method of generating monoclonal antibodies. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.
- Other suitable techniques involve selection of libraries of antibodies in phage or similar vectors.
- See, e.g., Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced. See, Cabilly, U.S.

Patent No. 4,816,567; and Queen, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033.

The antibodies of this invention are useful for affinity chromatography in isolating SOCS or WDS protein. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, SEPHADEX, or the like, where a cell lysate or supernatant may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby purified SOCS or WDS protein will be released.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies to SOCS or WDS proteins may be used for the identification of cell populations expressing the proteins. By assaying, e.g., by histology or otherwise, probably a disruptive assay which kills that sample of cells, the expression products of cells expressing SOCS or WDS proteins it is possible to diagnose disease, e.g., cancerous conditions.

Antibodies raised against each SOCS or WDS protein will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

B. Immunoassays

A particular protein can be measured by a variety of immunoassay methods. For a review of immunological and immunoassay procedures in general, see Stites and Terr (eds.) (1991) Basic and Clinical Immunology (7th ed.). Moreover, the immunoassays of the present invention can be performed in many configurations, which are reviewed extensively in Maggio (ed.) (1980) Enzyme Immunoassay CRC Press, Boca Raton, Florida; Tijan (1985) "Practice and Theory of Enzyme Immunoassays," Laboratory Techniques in

Biochemistry and Molecular Biology, Elsevier Science Publishers B.V., Amsterdam; and Harlow and Lane Antibodies, A Laboratory Manual, supra, each of which is incorporated herein by reference. See also Chan (ed.)

- 5 (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassays Stockton Press, NY; and Ngo (ed.) (1988) Non-isotopic Immunoassays Plenum Press, NY.

Immunoassays for measurement of SOCS or WDS proteins
10 can be performed by a variety of methods known to those skilled in the art. In brief, immunoassays to measure the protein can be either competitive or noncompetitive binding assays. In competitive binding assays, the sample to be analyzed competes with a labeled analyte for
15 specific binding sites on a capture agent bound to a solid surface. Preferably the capture agent is an antibody specifically reactive with SOCS or WDS proteins produced as described above. The concentration of labeled analyte bound to the capture agent is inversely
20 proportional to the amount of free analyte present in the sample.

In a competitive binding immunoassay, the SOCS or WDS protein present in the sample competes with labeled protein for binding to a specific binding agent, for
25 example, an antibody specifically reactive with the SOCS or WDS protein. The binding agent may be bound to a solid surface to effect separation of bound labeled protein from the unbound labeled protein. Alternately, the competitive binding assay may be conducted in liquid
30 phase and a variety of techniques known in the art may be used to separate the bound labeled protein from the unbound labeled protein. Following separation, the amount of bound labeled protein is determined. The amount of protein present in the sample is inversely
35 proportional to the amount of labeled protein binding.

Alternatively, a homogeneous immunoassay may be performed in which a separation step is not needed. In these immunoassays, the label on the protein is altered by the binding of the protein to its specific binding

- agent. This alteration in the labeled protein results in a decrease or increase in the signal emitted by label, so that measurement of the label at the end of the immunoassay allows for detection or quantitation of the protein.
- 5

Qualitative or quantitative analysis of SOCS or WDS proteins may also be determined by a variety of noncompetitive immunoassay methods. For example, a two-site, solid phase sandwich immunoassay may be used. In this type of assay, a binding agent for the protein, for example an antibody, is attached to a solid support. A second protein binding agent, which may also be an antibody, and which binds the protein at a different site, is labeled. After binding at both sites on the protein has occurred, the unbound labeled binding agent is removed and the amount of labeled binding agent bound to the solid phase is measured. The amount of labeled binding agent bound is directly proportional to the amount of protein in the sample.

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Western blot analysis can be used to determine the presence of SOCS or WDS proteins in a sample. Electrophoresis is carried out, for example, on a tissue sample suspected of containing the protein. Following electrophoresis to separate the proteins, and transfer of the proteins to a suitable solid support, e.g., a nitrocellulose filter, the solid support is incubated with an antibody reactive with the protein. This antibody may be labeled, or alternatively may be detected by subsequent incubation with a second labeled antibody that binds the primary antibody.

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The immunoassay formats described above employ labeled assay components. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels and methods may be used. Traditionally, a radioactive label incorporating ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P was used. Non-radioactive labels include proteins which bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair

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- members for a labeled protein. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation. For a review of various labeling or
- 5 signal producing systems which may be used, see U.S. Patent No. 4,391,904, which is incorporated herein by reference.

- Antibodies reactive with a particular protein can also be measured by a variety of immunoassay methods.
- 10 For a review of immunological and immunoassay procedures applicable to the measurement of antibodies by immunoassay techniques, see Stites and Terr (eds.) Basic and Clinical Immunology (7th ed.) supra; Maggio (ed.) Enzyme Immunoassay, supra; and Harlow and Lane
- 15 Antibodies, A Laboratory Manual, supra.

- In brief, immunoassays to measure antisera reactive with SOCS or WDS proteins can be either competitive or noncompetitive binding assays. In competitive binding assays, the sample analyte competes with a labeled
- 20 analyte for specific binding sites on a capture agent bound to a solid surface. Preferably the capture agent is a purified recombinant SOCS or WDS protein produced as described above. Other sources of these proteins, including isolated or partially purified naturally
- 25 occurring protein, may also be used. Noncompetitive assays include sandwich assays, in which the sample analyte is bound between two analyte-specific binding reagents. One of the binding agents is used as a capture agent and is bound to a solid surface. The second
- 30 binding agent is labeled and is used to measure or detect the resultant complex by visual or instrument means. A number of combinations of capture agent and labeled binding agent can be used. A variety of different immunoassay formats, separation techniques, and labels
- 35 can be also be used similar to those described above for the measurement of SOCS or WDS proteins.

V. Making SOCS or WDS proteins; Mimetics

- DNAs which encode a SOCS or WDS protein or fragments
- 40 thereof can be obtained by chemical synthesis, screening

cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Methods for doing so, or making expression vectors are described herein.

- 5 These DNAs can be expressed in a wide variety of host cells for the synthesis of a full-length protein or fragments which can in turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules; 10 and for structure/function studies. Each SOCS or WDS protein or its fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. By "transformed" is meant a cell into which (or into an ancestor of which) has been 15 introduced, by means of recombinant techniques, a DNA molecule that encodes a SOCS or WDS polypeptide. Heterologously expressed SOCS or WDS polypeptides can be substantially purified to be free of protein or cellular contaminants, other than those derived from the 20 recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The antigen, e.g., SOCS or WDS protein, or portions thereof, may be expressed as fusions with other proteins or 25 possessing an epitope tag.

- Expression vectors are typically self-replicating DNA or RNA constructs containing the desired antigen gene or its fragments, usually operably linked to appropriate genetic control elements that are recognized in a 30 suitable host cell. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control 35 system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that 40 terminate transcription and translation. All of the

associated elements both necessary and sufficient for the production of SOCS or WDS polypeptide will be in operable linkage with the nucleic acid encoding a SOCS or WDS polypeptide. Expression vectors also usually contain an
5 origin of replication that allows the vector to replicate independently from the host cell.

The vectors of this invention contain DNAs which encode a SOCS or WDS protein, or a fragment thereof, typically encoding, e.g., a biologically active
10 polypeptide, or protein. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for a SOCS or WDS protein in a
15 prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the protein is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are
20 designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient
25 expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of a SOCS or WDS protein gene or its fragments into the host DNA by
30 recombination, or to integrate a promoter which controls expression of an endogenous gene.

Vectors, as used herein, contemplate plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA
35 fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector, but many other forms of vectors which serve an
40 equivalent function are suitable for use herein. See,

e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual Elsevier, N.Y.; and Rodriguez, et al. (eds.) (1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses Buttersworth,

5 Boston, MA.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., *E. coli* and *B. subtilis*. Lower eukaryotes include yeasts, 10 e.g., *S. cerevisiae* and *Pichia*, and species of the genus *Dictyostelium*. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

15 Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, *E. coli* and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or 20 its derivatives. Vectors that can be used to express these proteins or protein fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters 25 (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez and Denhardt (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses 10:205-236 30 Buttersworth, Boston, MA.

Lower eukaryotes, e.g., yeasts and *Dictyostelium*, may be transformed with SOCS or WDS protein sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, 35 *Saccharomyces cerevisiae*. It will be used generically to represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA

- encoding the desired protein or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as
- 5 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such
- 10 as the YRp-series), self-replicating high copy number (such as the YEpl-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

- Higher eukaryotic tissue culture cells are typically
- 15 the preferred host cells for expression of the functionally active SOCS or WDS protein. In principle, many higher eukaryotic tissue culture cell lines may be used, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source.
- 20 However, mammalian cells are preferred to achieve proper processing, both cotranslationally and posttranslationally. Transformation or transfection and propagation of such cells is routine. Useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell
- 25 lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (e.g., if genomic DNA
- 30 is used), a polyadenylation site, and a transcription termination site. These vectors also may contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such
- 35 sources as adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503-
- 40 512; and a baculovirus vector such as pAC 373 or pAC 610.

It is likely that SOCS or WDS proteins need not be glycosylated to elicit biological responses. However, it will occasionally be desirable to express a SOCS or WDS protein polypeptide in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., in unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the SOCS or WDS protein gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. It is further understood that over glycosylation may be detrimental to SOCS or WDS protein biological activity, and that one of skill may perform routine testing to optimize the degree of glycosylation which confers optimal biological activity.

Furthermore, heterologously expressed proteins or polypeptides can also be expressed in plant cells. For plant cells viral expression vectors (e.g., cauliflower mosaic virus and tobacco mosaic virus) and plasmid expression vectors (e.g., T1 plasmid) are suitable. Such cells are available from a wide range of sources (e.g., the American Tissue Type Culture Collection, Rockland, MD; also, see for example, Ausubel, et al. (cur. ed. and Supplements; expression vehicles may be chosen from those provided e.g., in Pouwels, et al. (Cur. ed.) Cloning Vectors, A Laboratory Manual).

A SOCS or WDS protein, or a fragment thereof, may be engineered to be phosphatidyl inositol (PI) linked to a cell membrane, but can be removed from membranes by treatment with a phosphatidyl inositol cleaving enzyme, e.g., phosphatidyl inositol phospholipase-C. This releases the antigen in a biologically active form, and allows purification by standard procedures of protein chemistry. See, e.g., Low (1989) Biochem. Biophys. Acta 988:427-454; Tse, et al. (1985) Science 230:1003-1008; and Brunner, et al. (1991) J. Cell Biol. 114:1275-1283.

Now that SOCS or WDS proteins have been characterized, fragments or derivatives thereof can be

prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis Springer-Verlag, New York, NY; and Bodanszky (1984) The Principles of Peptide Synthesis Springer-Verlag, New York, NY. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimide process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The SOCS or WDS proteins of this invention can be obtained in varying degrees of purity depending upon its desired use. Purification can be accomplished by use of known protein purification techniques or by the use of the antibodies or binding partners herein described, e.g., in immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the SOCS or WDS proteins as a result of recombinant DNA techniques, see below.

Multiple cell lines may be screened for one which expresses a SOCS or WDS protein at a high level compared with other cells. Various cell lines, e.g., a mouse thymic stromal cell line TA4, is screened and selected for its favorable handling properties. Natural SOCS or WDS proteins can be isolated from natural sources, or by

- expression from a transformed cell using an appropriate expression vector. Purification of the expressed protein is achieved by standard procedures, or may be combined with engineered means for effective purification at high efficiency from cell lysates or supernatants. Epitope or other tags, e.g., FLAG or His₆ segments, can be used for such purification features.

VI. Physical Variants

- 10 This invention also encompasses proteins or peptides having substantial amino acid sequence similarity with an amino acid sequence of a SOCS or WDS protein. Natural variants include individual, polymorphic, allelic, strain, or species variants.
- 15 Amino acid sequence similarity, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. This changes when considering conservative substitutions as matches. Conservative substitutions typically include
- 20 substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences include natural
- 25 polymorphic, allelic, and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 50-100% similarity (if gaps can be introduced), to 75-100% similarity (if conservative substitutions are included) over fixed
- 30 stretches of amino acids with the amino acid sequence of the SOCS or WDS protein. Similarity measures will be at least about 50%, generally at least 65%, usually at least 70%, preferably at least 75%, and more preferably at least 90%, and in particularly preferred embodiments, at
- 35 least 96% or more. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison Chapter One, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin

- Genetics Computer Group, Madison, WI. Stretches of amino acids will be at least about 10 amino acids, usually about 20 amino acids, usually 50 amino acids, preferably 75 amino acids, and in particularly preferred embodiments at least about 100 amino acids. Identity can also be measures over amino acid stretches of about 98, 99, 110, 120, 130, etc.

- Nucleic acids encoding mammalian SOCS or WDS proteins will typically hybridize to the nucleic acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15 under stringent conditions. For example, nucleic acids encoding human SOCS or WDS proteins will normally hybridize to the nucleic acid of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15 under stringent hybridization conditions. Generally, stringent conditions are selected to be about 10° C lower than the thermal melting point (T_m) for the probe sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Typically, stringent conditions will be those in which the salt concentration is about 0.2 molar at pH 7 and the temperature is at least about 50° C. Other factors may significantly affect the stringency of hybridization, including, among others, base composition and size of the complementary strands, the presence of organic solvents such as formamide, and the extent of base mismatching. A preferred embodiment will include nucleic acids which will bind to disclosed sequences in 50% formamide and 200 mM NaCl at 42° C.

- Hybridizing nucleic acids to SOCS nucleic acid of the invention can be used as a cloning probe, a primer (e.g., a PCR primer), or a diagnostic probe. Hybridizing nucleic acids can be splice variants encoded by one of the SOCS genes described herein. Thus, the hybridizing nucleic acids may encode a polypeptide that is shorter or longer than the various forms of SOCS described herein. Hybridizing nucleic acids may also encode proteins that are related to SOCS (e.g., polypeptides encoded by genes

that include a portion having a relatively high degree of identity to a SOCS gene described herein).

An isolated SOCS or WDS protein encoding DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and short inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode SOCS or WDS protein antigens, their derivatives, or proteins having highly similar physiological, immunogenic, or antigenic activity.

Modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant SOCS or WDS protein derivatives include predetermined or site-specific mutations of the respective protein or its fragments. "Mutant SOCS or WDS protein" encompasses a polypeptide otherwise falling within the homology definition of the human or rodent SOCS or WDS protein as set forth above, but having an amino acid sequence which differs from that of a SOCS or WDS protein as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant SOCS or WDS protein" generally includes proteins having significant similarity with a protein having a sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16, e.g., natural embodiments, and as sharing various biological activities, e.g., antigenic or immunogenic, with those sequences, and in preferred embodiments contain most or all of the disclosed sequence. This applies also to polymorphic variants from different individuals. Similar concepts apply to different SOCS or WDS proteins, particularly those found in various warm blooded animals, e.g., mammals and birds. As stated before, it is emphasized that descriptions are generally meant to encompass other SOCS or WDS proteins, not limited to the human embodiments specifically discussed.

The invention encompasses, but is not limited to, SOCS proteins and polypeptides that are functionally related to SOCS encoded by the specific sequence

identifiers of the present application. Functionally related proteins and polypeptides include any protein or polypeptide sharing a functional characteristic with SOCS of the present invention e.g., the ability to interact with Janus family tyrosine kinases or the ability to be induced by IL-2 receptor activation. Such functionally related SOCS polypeptides include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the SOCS sequences described herein which result in a silent change, thus producing a functionally equivalent SOCS polypeptide. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphiphatic nature of the residues involved.

For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

While random mutations can be made to SOCS nucleic acid (using well known random mutagenesis techniques) and the resulting SOCS polypeptides can be tested for activity, site-directed mutations of SOCS coding sequences can be engineered (using well known site-directed mutagenesis techniques) to generate mutant SOCS with increased function, e.g. greater inhibition of JANUS kinase activity or greater resistance to degradation.

To design functionally related and functionally variant SOCS polypeptides, it is useful to distinguish between conserved and variable amino residues using the homology comparison tables provided herein.

To preserve SOCS function, it is preferable that conserved residues remain unaltered and that the conformational folding of the SOCS functional sites be preserved. Preferably, alteration of non-conserved residues are carried out with conservative alterations

- e.g., a basic amino acid is replaced by a different basic amino acid. To produce altered function variants, it is preferred to make non-conservative changes at variable and or conserved residues. Deletions at conserved and
- 5 variable residues can also be used to create altered function variants.

- Although site specific mutation sites are predetermined, mutants need not be site specific. SOCS or WDS protein mutagenesis can be conducted by making
- 10 amino acid insertions or deletions. Substitutions, deletions, insertions, or any combinations may be generated to arrive at a final construct. Insertions include amino- or carboxyl- terminal fusions, e.g. epitope tags. Random mutagenesis can be conducted at a
- 15 target codon and the expressed mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis or polymerase chain reaction
- 20 (PCR) techniques. See also, Sambrook, et al. (1989) and Ausubel, et al. (1987 and Supplements). The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce
- 25 secondary mRNA structure such as loops or hairpins.

- The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are
- 30 naturally not normally fused in the same manner e.g., a marker polypeptide or fusion partner. For example, the polypeptide can be fused to a hexa-histidine tag to facilitate purification or bacterially expressed protein or a hemagglutinin tag to facilitate purification or
- 35 protein expressed in eukaryotic cells. Thus, the fusion product of an immunoglobulin with a SOCS or WDS protein polypeptide is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting

properties derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

- In addition, new constructs may be made from combining similar functional domains from other proteins.
- 5 For example, protein-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992. Thus, new chimeric polypeptides
- 10 exhibiting new combinations of specificities will result from the functional linkage of protein-binding specificities and other functional domains.

VII. Functional Variants

- 15 The blocking of physiological response to SOCS or WDS protein may result from the inhibition of binding of the protein to its binding partner, e.g., through competitive inhibition. Thus, in vitro assays of the present invention will often use isolated protein,
- 20 membranes from cells expressing a recombinant membrane associated SOCS or WDS protein, soluble fragments comprising binding segments of these proteins, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination
- 25 of the effects of either binding segment mutations and modifications, or protein mutations and modifications, e.g., protein analogs. This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to antigen or binding partner
- 30 fragments compete with a test compound for binding to the protein. In this manner, the antibodies can be used to detect the presence of a polypeptide which shares one or more antigenic binding sites of the protein and can also be used to occupy binding sites on the protein that might
- 35 otherwise interact with a binding partner.

"Derivatives" of SOCS or WDS protein antigens include amino acid sequence mutants, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared

40 by linkage of functionalities to groups which are found

in SOCS or WDS protein amino acid side chains or at the N- or C- termini, by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or
5 of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of
10 alkyl-moieties including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species. Covalent attachment to carrier proteins may be important when immunogenic moieties are haptens.

In particular, glycosylation alterations are
15 included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from
20 cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid
25 residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine, or other moieties, including ribosyl groups or cross-linking reagents.

A major group of derivatives are covalent conjugates of the SOCS or WDS protein or fragments thereof with
30 other proteins or polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred protein derivatization
35 sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between SOCS or WDS protein and other homologous or heterologous proteins are also provided. Heterologous polypeptides may be fusions
40 between different surface markers, resulting in, e.g., a

- hybrid protein exhibiting binding partner specificity. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions
- 5 of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a segment involved in binding partner interaction, so that the presence or location of the fused protein may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609.
- 10 Other gene fusion partners include bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. The fusion partner can be constructed such
- 15 that it can be cleaved off such that a protein of substantially natural length is generated.

- Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of
- 20 other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity proteins.

- This invention also contemplates the use of
- 25 derivatives of SOCS or WDS protein other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into the three classes: (1) salts, (2)
- 30 side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of
- 35 proteinss or other binding proteins. For example, a SOCS or WDS protein antigen can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated SEPHAROSE, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or
- 40 without glutaraldehyde cross-linking, for use in the

assay or purification of anti-SOCS or anti-WDS protein antibodies or its respective binding partner. The SOCS or WDS protein can also be labeled with a detectable group, e.g., radioiodinated by the chloramine T

- 5 procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays. Purification of SOCS or WDS proteins may be effected by immobilized antibodies or binding partner.

- 10 Isolated SOCS or WDS protein genes will allow transformation of cells lacking expression of corresponding SOCS or WDS protein, e.g., either species types or cells which lack corresponding proteins and exhibit negative background activity. Expression of
- 15 transformed genes will allow isolation of antigenically pure cell lines, with defined or single species variants. This approach will allow for more sensitive detection and discrimination of the physiological effects of SOCS or WDS binding proteins. Subcellular fragments, e.g.,
- 20 cytoplasts or membrane fragments, can be isolated and used.

VIII. Binding Agent:SOCS or :WDS Protein Complexes

- A SOCS or WDS protein that specifically binds to or
- 25 that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 is typically determined in an immunoassay. The immunoassay uses a polyclonal
- 30 antiserum which was raised to a protein of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16. This antiserum is selected to have low crossreactivity against other intracellular regulatory proteins and any such crossreactivity is removed by immunoabsorption prior to use in the
- 35 immunoassay.

- In order to produce antisera for use in an immunoassay, the protein of desired sequence, e.g., SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and/or 16, is isolated as described herein. For example, recombinant protein may
- 40 be produced in a mammalian cell line. An inbred strain

of mice such as Balb/c is immunized with the protein of appropriate sequence using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide, preferably near full length, derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, for example, a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other intracellular proteins, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably two intracellular proteins are used in this determination in conjunction with the desired SOCS or WDS protein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, a protein of SEQ ID NO: 2 or 4 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 2 or 4. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the SOCS14 or SOCS15 protein of SEQ ID NO: 2 and 6, or 4). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the

immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein, e.g., of SEQ ID NO: 2 that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that each of SOCS or WDS proteins are members of respective families of homologous proteins that comprise two or more genes. For a particular gene product, such as the human SOCS14 or SOCS15 protein, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are polymorphic, allelic, non-allelic, or species variants. It is also understood that the term "SOCS14 or SOCS15 protein" includes nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding SOCS14 or SOCS15 proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations should substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring SOCS or WDS protein, for example, the human SOCS14 or SOCS15 protein shown in SEQ ID NO: 2 and 6, or 4 and 8. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring, e.g., a proliferative effect. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the SOCS14 or SOCS15 protein as a whole. By aligning a protein optimally with the protein of SEQ ID NO: 2, 4, 6, or 8, and by using the conventional immunoassays described herein to determine immunoidentity, or by using proliferative assays, one can determine the protein compositions of the invention.

IX. Uses

The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for
5 developmental abnormalities, or below in the description of kits for diagnosis. Moreover, the SOCS proteins can block signaling via cytokine receptors.

SOCS or WDS nucleotides, e.g., human SOCS14 or SOCS15 DNA or RNA, may be used as a component in a
10 forensic assay. For instance, the nucleotide sequences provided may be labeled using, e.g., ³²P or biotin and used to probe standard restriction fragment polymorphism blots, providing a measurable character to aid in
distinguishing between individuals. Such probes may be
15 used in well-known forensic techniques such as genetic fingerprinting. In addition, nucleotide probes made from SOCS or WDS sequences may be used in in situ assays to detect chromosomal abnormalities. For instance, rearrangements in the human chromosome encoding a SOCS14
20 or SOCS15 gene may be detected via well-known in situ techniques, using SOCS14 or SOCS15 probes in conjunction with other known chromosome markers.

Antibodies and other binding agents directed towards SOCS or WDS proteins or nucleic acids may be used to
25 purify the corresponding SOCS or WDS molecule. As described in the Examples below, antibody purification of SOCS or WDS protein components is both possible and practicable. Antibodies and other binding agents may also be used in a diagnostic fashion to determine whether
30 SOCS or WDS protein components are present in a tissue sample or cell population using well-known techniques described herein. The ability to attach a binding agent to a SOCS or WDS protein provides a means to diagnose disorders associated with SOCS or WDS protein
35 misregulation. Antibodies and other SOCS or WDS protein binding agents may also be useful as histological markers. It is likely that specific SOCS or WDS protein expression is limited to specific tissue types. By directing a probe, such as an antibody or nucleic acid to
40 a SOCS14 or SOCS15 protein it is possible to use the

probe to distinguish tissue and cell types in situ or in vitro.

This invention also provides reagents with significant therapeutic value. The SOCS or WDS protein (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to a SOCS or WDS protein, are useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a SOCS or WDS protein is a target for an agonist or antagonist of the protein. The proteins likely play a role in regulation or development of neuronal or hematopoietic cells, e.g., lymphoid cells, which affect immunological responses.

For example, SOCS or WDS proteins likely play a role in T cell activation deficiencies in which patients develop clinical manifestations of T cell immunodeficiency such as opportunistic infections, recurrent viral or bacterial infections, diarrhea, autoimmune hemolytic anemia, lymphoid hepatitis and dermatitis, and Hodgkin lymphoma, at various stages of childhood. An excess of SOCS proteins might lead to SCID-like (severe combined immunodeficiencies) syndromes while a deficit of SOCS or WDS proteins may lead to malignant growth, for example, adult T cell leukemia/lymphoma is a disease associated with uncontrolled T-cell proliferation and is correlated at the molecular level with the presence of the IL-2 receptor (Schechter, G.P.; "Chronic Lymphocytic Leukemia" in Clinical Immunology: Principles and Practice, Rich (ed.) Mosby, St. Louis (Curr. ed.)). A model for adult T cell leukemia suggests that the disease may result from constitutive activation of the IL-2 receptor and its subsequent constitutive signaling cascade.

Administration of exogenous SOCS to effected T cells may modulate this disease.

- Other abnormal developmental conditions are known in cell types shown to possess SOCS or WDS protein mRNA by northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, N.J.; Thorn et al. Harrison's Principles of Internal Medicine, McGraw-Hill, N.Y.; and Rich (ed.) Clinical Immunology: Principles and Practice, Mosby, St. Louis
- 10 (Curr. ed.). Developmental or functional abnormalities, e.g., of the neuronal or immune system, cause significant medical abnormalities and conditions which may be susceptible to prevention or treatment using compositions provided herein.
- 15 Recombinant SOCS or WDS protein or SOCS or WDS antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or
- 20 diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This
- 25 invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

- Drug screening using antibodies or fragments thereof can identify compounds having binding affinity to SOCS or
- 30 WDS protein, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the protein.
- 35 Likewise, a compound having intrinsic stimulating activity can activate the binding partner and is thus an agonist in that it simulates the activity of a SOCS or WDS protein. This invention further contemplates the therapeutic use of antibodies to SOCS or WDS protein as

antagonists. This approach should be particularly useful with other SOCS or WDS protein species variants.

- Another therapeutic approach included within the invention involves direct administration of reagents or compositions by any conventional administration techniques (for example but not restricted to local injection, inhalation, or administered systemically), to the subject with an immune, allergic or trauma disorder. The reagents, formulations or compositions included within the bounds and metes of the invention may also be targeted to specific cells by any of the methods described herein. The actual dosage of reagent, formulation or composition that modulates an immune, disorder depends on many factors, including the size and health of an organism, however one of one of ordinary skill in the art can use the following teachings describing the methods and techniques for determining clinical dosages. Spilker (1984) Guide to Clinical Studies and Developing Protocols, Raven Press Books, Ltd., New York, pp. 7-13, 54-60; Spilker (1991) Guide to Clinical Trials, Raven Press, Ltd., New York, pp. 93-101; Craig and Stitzel (eds. 1986) Modern Pharmacology, 2d ed., Little, Brown and Co., Boston, pp. 127-33; Speight (ed. 1987) Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3d ed., Williams and Wilkins, Baltimore, pp. 50-56; Tallarida, et al. (1988) Principles in General Pharmacology, Springer-Verlag, New York, pp. 18-20) to determine the appropriate dosage to use; but, generally, in the range of about between 0.5 fg/ml and 500 µg/ml inclusive final concentration are administered per day to an adult in any pharmaceutically-acceptable carrier.

- The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents.

- Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, NJ. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous administration.
- SOCS or WDS protein, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in any conventional dosage formulation. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including

- subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g.,
- 5 Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral
- 10 Medications Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association
- 15 with other therapeutic agents.

- Both the naturally occurring and the recombinant forms of the SOCS or WDS proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to
- 20 the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period. See, e.g., Fodor, et al. (1991) Science 251:767-773, and other descriptions of chemical diversity libraries, which
- 25 describe means for testing of binding affinity by a plurality of compounds. The development of suitable assays can be greatly facilitated by the availability of large amounts of purified, soluble SOCS or WDS protein as provided by this invention.

- 30 For example, antagonists can normally be found once the protein has been structurally defined. Testing of potential protein analogs is now possible upon the development of highly automated assay methods using a purified binding partner. In particular, new agonists
- 35 and antagonists will be discovered by using screening techniques described herein. Of particular importance are compounds found to have a combined binding affinity for multiple SOCS or WDS protein binding components, e.g., compounds which can serve as antagonists for
- 40 species variants of a SOCS or WDS protein.

This invention is particularly useful for screening compounds by using recombinant protein in a variety of drug screening techniques. The advantages of using a recombinant protein in screening for specific binding partners include: (a) improved renewable source of the SOCS or WDS protein from a specific source; (b) potentially greater number of binding partners per cell giving better signal to noise ratio in assays; and (c) species variant specificity (theoretically giving greater biological and disease specificity).

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing a SOCS or WDS protein binding counterpart. Cells may be isolated which express a binding counterpart in isolation from any others. Such cells, either in viable or fixed form, can be used for standard protein binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of SOCS14 or SOCS15 protein) are contacted and incubated with a labeled binding partner or antibody having known binding affinity to the protein, such as ¹²⁵I-antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of protein binding. The amount of test compound bound is inversely proportional to the amount of labeled binding partner binding to the known source. Any one of numerous techniques can be used to separate bound from free protein to assess the degree of protein binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on SOCS or WDS protein mediated functions, e.g., second messenger levels, i.e., cell proliferation; inositol phosphate pool changes, transcription using a luciferase-type assay; and

others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system.

Another method utilizes membranes from transformed eukaryotic or prokaryotic host cells as the source of a SOCS or WDS protein. These cells are stably transformed with DNA vectors directing the expression of a SOCS or WDS protein, e.g., an engineered membrane bound form. Essentially, the membranes would be prepared from the cells and used in a protein binding assay such as the competitive assay set forth above.

Still another approach is to use solubilized, unpurified or solubilized, purified SOCS or WDS protein from transformed eukaryotic or prokaryotic host cells. This allows for a "molecular" binding assay with the advantages of increased specificity, the ability to automate, and high drug test throughput.

Another technique for drug screening involves an approach which provides high throughput screening for compounds having suitable binding affinity to a SOCS or WDS protein antibody and is described in detail in Geysen, European Patent Application 84/03564, published on September 13, 1984. First, large numbers of different small peptide test compounds are synthesized on a solid substrate, e.g., plastic pins or some other appropriate surface, see Fodor, et al., supra. Then all the pins are reacted with solubilized, unpurified or solubilized, purified SOCS or WDS protein antibody, and washed. The next step involves detecting bound SOCS or WDS protein antibody.

Rational drug design may also be based upon structural studies of the molecular shapes of the SOCS or WDS protein and other effectors or analogs. See, e.g., Methods in Enzymology vols 202 and 203. Effectors may be other proteins which mediate other functions in response to protein binding, or other proteins which normally interact with the binding partner. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques.

These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crvstallography

5 Academic Press, NY.

A purified SOCS or WDS protein can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture
10 antibodies to immobilize the respective protein on the solid phase.

X. Kits

This invention also contemplates use of SOCS or WDS
15 proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of SOCS or WDS protein or a binding partner. Typically the kit will have a compartment containing either a defined SOCS or WDS
20 protein peptide or gene segment or a reagent which recognizes one or the other, e.g., binding partner fragments or antibodies.

A kit for determining the binding affinity of a test compound to a SOCS or WDS protein would typically
25 comprise a test compound; a labeled compound, e.g., a binding agent or antibody having known binding affinity for the SOCS or WDS protein; a source of SOCS or WDS protein (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as
30 a solid phase for immobilizing the SOCS or WDS protein. Once compounds are screened, those having suitable binding affinity to the SOCS or WDS protein can be evaluated in suitable biological assays, as are well known in the art, to determine whether they act as
35 agonists or antagonists to the binding partner. The availability of recombinant SOCS or WDS protein polypeptides also provide well defined standards for calibrating such assays.

A preferred kit for determining the concentration
40 of, for example, a SOCS or WDS protein in a sample would

- typically comprise a labeled compound, e.g., binding partner or antibody, having known binding affinity for the SOCS or WDS protein, a source of SOCS or WDS protein (naturally occurring or recombinant), and a means for
- 5 separating the bound from free labeled compound, for example, a solid phase for immobilizing the SOCS or WDS protein. Compartments containing reagents, and instructions, will normally be provided.

- Antibodies, including antigen binding fragments, specific for the SOCS or WDS protein or fragments thereof are useful in diagnostic applications to detect the presence of elevated levels of SOCS or WDS protein and/or its fragments. Such diagnostic assays can employ lysates, live cells, fixed cells, immunofluorescence,
- 15 cell cultures, body fluids, and further can involve the detection of antigens related to the protein in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and antigen-SOCS or -WDS protein complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA), and
- 25 the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a SOCS or WDS protein or to a particular fragment thereof. Similar assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press, NY; Chan (ed.) (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassay Stockton Press, NY; and Ngo (ed.) (1988) Nonisotopic Immunoassay Plenum Press, NY.
- 30
- 35

- Anti-idiotypic antibodies may have similar use to diagnose presence of antibodies against a SOCS or WDS protein, as such may be diagnostic of various abnormal states. For example, overproduction of SOCS or WDS
- 40 protein may result in production of various immunological

or other medical reactions which may be diagnostic of abnormal physiological states, e.g., in cell growth, activation, or differentiation.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody or binding partner, or labeled SOCS or WDS protein is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium providing appropriate concentrations of reagents for performing the assay.

Many of the aforementioned constituents of the drug screening and the diagnostic assays may be used without modification, or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In any of these assays, the protein, test compound, SOCS or WDS protein, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free protein, or alternatively the bound from the free test compound. The SOCS or WDS protein can

- be immobilized on various matrices followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the SOCS or WDS protein to a matrix include, without limitation,
- 5 direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of protein/binding partner or antigen/antibody complex by any of several methods including those utilizing, e.g.,
- 10 an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the
- 15 double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678.

- Methods for linking proteins or their fragments to the various labels have been extensively reported in the literature and do not require detailed discussion here.
- 20 Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated
- 25 olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

- Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of a SOCS or WDS protein. These
- 30 sequences can be used as probes for detecting levels of the SOCS or WDS protein message in samples from natural sources, or patients suspected of having an abnormal condition, e.g., cancer or developmental problem. The preparation of both RNA and DNA nucleotide sequences, the
- 35 labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes
- 40 may be up to several kilobases. Various labels may be

employed, most commonly radionuclides, particularly ³²P. However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorophores, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out using many conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLES

I. General Methods

- 5 Many of the standard methods below are described or referenced, e.g., in Maniatis, et al. (Cur. ed.) Molecular Cloning, A Laboratory Manual Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.) Vols. 1-3, CSH Press, NY; Ausubel, et al., Biology Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology Wiley/Greene, NY; Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications Academic Press, NY. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification," Methods in Enzymology vol. 182, and other volumes in this series; Coligan, et al. (1995 and supplements) Current Protocols in Protein Science John Wiley and Sons, New York, NY; P. Matsudaira (ed.) (1993) A Practical Guide to Protein and Peptide Purification for Microsequencing, Academic Press, San Diego, CA; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, NJ, or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments (epitope tags), e.g., to a FLAG sequence or an equivalent which can be fused, e.g., via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, NY; and Crowe, et al. (1992) OTaexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.
- 35 Standard immunological techniques are described,
- 40 e.g., in Hertenzenberg, et al. (eds. 1996) Weir's Handbook

- of Experimental Immunology vols 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163. Assays for neural cell biological activities are described, e.g., in Wouterlood (ed. 1995) Neuroscience Protocols modules 10, Elsevier; Methods in Neurosciences Academic Press; and Neuromethods Humana Press, Totowa, NJ. Methodology of developmental systems is described, e.g., in Meisami (ed.) Handbook of Human Growth and Developmental Biology CRC Press; and Chrispeels (ed.) Molecular Techniques and Approaches in Developmental Biology Interscience.
- FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY.
- II. Isolation of full length SOCS or WDS clones
- Standard methods are used to isolate full length genes. A cDNA library from an appropriate, e.g., human, cell, preferably a STAT containing cell type. The appropriate sequence is selected, and hybridization at high stringency conditions is performed to find a full length corresponding gene. It is noted that the mouse and human protein sequences are virtually identical.
- III. Isolation of primate SOCS14 or SOCS15 clones
- The full length, or appropriate fragments, of human genes are used to isolate a corresponding monkey or other primate gene. Preferably a full length coding sequence is used for hybridization. Similar source materials as indicated above are used to isolate natural genes, including genetic, polymorphic, allelic, or strain variants. Other species variants are also isolated using similar methods.

IV. Isolation of an avian SOCS14 or SOCS15 clone

An appropriate avian source is selected as above. Similar methods are utilized to isolate a species variant, though the level of similarity will typically be lower for an avian protein as compared to a human to mouse sequence.

V. Expression; purification; characterization

Proteins of interest are immunoprecipitated and affinity purified as described above, e.g., from a natural or recombinant source.

Alternatively, with an appropriate clone from above, the coding sequence is inserted into an appropriate expression vector. This may be in a vector specifically selected for a prokaryote, yeast, insect, or higher vertebrate, e.g., mammalian expression system. Standard methods are applied to produce the gene product, preferably as a soluble secreted molecule, but will, in certain instances, also be made as an intracellular protein. Intracellular proteins typically require cell lysis to recover the protein, and insoluble inclusion bodies are a common starting material for further purification.

With a clone encoding a vertebrate SOCS14 or SOCS15 protein, recombinant production means are used, although natural forms may be purified from appropriate sources. The protein product is purified by standard methods of protein purification, in certain cases, e.g., coupled with immunoaffinity methods. Immunoaffinity methods are used either as a purification step, as described above, or as a detection assay to determine the separation properties of the protein.

Preferably, the protein is secreted into the medium, and the soluble product is purified from the medium in a soluble form. Alternatively, as described above, inclusion bodies from prokaryotic expression systems are a useful source of material. Typically, the insoluble protein is solubilized from the inclusion bodies and refolded using standard methods. Purification methods are developed as described above.

The product of the purification method described above is characterized to determine many structural features. Standard physical methods are applied, e.g., amino acid analysis and protein sequencing. The
5 resulting protein is subjected to CD spectroscopy and other spectroscopic methods, e.g., NMR, ESR, mass spectroscopy, etc. The product is characterized to determine its molecular form and size, e.g., using gel chromatography and similar techniques. Understanding of
10 the chromatographic properties will lead to more gentle or efficient purification methods.

Prediction of glycosylation sites may be made, e.g., as reported in Hansen, et al. (1995) Biochem. J. 308:801-813. However, as intracellular proteins, they are
15 unlikely to be normally glycosylated.

The purified protein is also be used to identify other binding partners of SOCS or WDS as described, e.g., in Fields and Song (1989) Nature 340:245-246.

20 VI. Preparation of antibodies against vertebrate SOCS or WDS

With protein produced, as above, animals are immunized to produce antibodies. Polyclonal antiserum is raised using non-purified antigen, though the resulting
25 serum will exhibit higher background levels. Preferably, the antigen is purified using standard protein purification techniques, including, e.g., affinity chromatography using polyclonal serum indicated above. Presence of specific antibodies is detected using defined
30 synthetic peptide fragments.

Polyclonal serum is raised against a purified antigen, purified as indicated above, or using, e.g., a plurality of, synthetic peptides. A series of overlapping synthetic peptides which encompass all of the
35 full length sequence, if presented to an animal, will produce serum recognizing most linear epitopes on the protein. Such an antiserum is used to affinity purify protein, which is, in turn, used to introduce intact full length protein into another animal to produce another
40 antiserum preparation.

Similar techniques are used to generate induce monoclonal antibodies to either unpurified antigen, or, preferably, purified antigen.

5 VII. Cellular and tissue distribution

Distribution of the protein or gene products are determined, e.g., using immunohistochemistry with an antibody reagent, as produced above, by Western blotting of cell lysates, or by screening for nucleic acids encoding the respective protein. Either hybridization or 10 PCR methods are used to detect DNA, cDNA, or message content. Histochemistry allows determination of the specific cell types within a tissue which express higher or lower levels of message or DNA. Antibody techniques 15 are useful to quantitate protein in a biological sample, including a liquid or tissue sample. Immunoassays are developed to quantitate protein. Also FACS analysis may be used to evaluate expression in a cell population. Appropriate tissue samples or cell types are isolated and 20 prepared for such detection. Commercial tissue blots are available, e.g., from Clontech (Mountain View, CA). Alternatively, cDNA library Southern blots can be analyzed.

25 VIII. STAT interference by SOCS or WDS proteins

Standard methods for testing the biological activity of the SOCS gene products in STAT signaling are described, e.g., in Starr, et al. (1997) Nature 387:917-921; Endo, et al. (1997) Nature 387:921-924; and Naka, et al. 30 Nature 387:924-929. Alternatively, JAK/STATs are necessary for signal transduction. This assay is performed as described, e.g., in Ho, et al. (1995) Mol. Cell. Biol. 15:5043-5-53, and blockage with these gene products may be tested.

35 In particular, the STAT5 dependent signaling in response to IL-2 is inhibited by the SOCS family member SOCS3.

IX. Antagonists of SOCS function

The inhibition of SOCS function may be effected by inhibitors of the specific interaction of these gene products and their respective STAT molecules. With the information on the specificity of pairings between these SOCS and respective STAT family members, compound libraries may be screened for blockage of such interactions. Thus, inhibitory action of the SOCS may be blocked with small molecule drug candidates.

- 10 Methods of using gene therapy are described, e.g., in Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989)
- 15 Science 244:1288; Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199. Also included is the use of antisense RNA in gene therapy to block expression of the target gene, or
- 20 proper splicing of gene transcripts.

X. Comparison of various SOCS embodiments

Tables 1 and 2 show comparison of various SOCS or WDS embodiments. Table 1 shows comparisons of the relevant portions of the gene products, particularly in the region of SOCS14 from Met168 to Leu293.

- Table 2 shows alignment of the WDS "SOCSBOX protein" with a consensus of the mouse and human SOCS15 (WDS11) protein sequences, which are identical. See GenBank
- 30 Accession numbers U88325; U88326; U88327; U88328; AB000676; AB000677; AB000710. This is aligned with the new WDS12, SEQ ID NO: 16.

Table 1: Comparison of various SOCS family members. mCIS is SEQ ID NO: 15; hSOCS1 is SEQ ID NO: 16; mSOCS1 is SEQ ID NO: 17; hSOCS2 is SEQ ID NO: 18; hSOCS3 is SEQ ID NO: 19; mSOCS3 is SEQ ID NO: 20; and human SOCS16 is SEQ ID NO: 21.

5	mCIS	
	hSOCS1	
	mSOCS1	
	hSOCS2	
10	hSOCS3	
	mSOCS3	
	hSOCS14	MEVRVKALVHSSS
	mSOCS17	AELGETR-----PESAQKKLPLRKA
	hSOCS18	MDKVGKMWNNLKYRCQNLF SHEGGSRNENVMNPRCPSPVKEKISISLGEA
15	hSOCS19	ERGLETNCSCEELSSPGRGGGGGRLLQ
	mCIS	
	hSOCS1	
20	mSOCS1	ALSPAATLTAWPADSARRGP-----
	hSOCS2	
	hSOCS3	
	mSOCS3	
	hSOCS14	PSPALNGVRKDFHDLQSETTCQEQANSKSSASHNGDLHLHLDEHVPVVI
25	mSOCS17	EN-----TIFITLEIVKNLFKMAENNSKNVDVRPKTSRSRAD-
	hSOCS18	APQQESSPLRENVALQLGLSPSKTFSRRNQNCAAEIPQVVEISIEKSDSDS
	hSOCS19	PGPELFPVPPFLQDLVPLGRLSRGEQQQQQQQPPPPPPPGPLRPLAG
	mCIS	
30	hSOCS1	
	mSOCS1	
	hSOCS2	-----
	hSOCS3	
35	mSOCS3	
	hSOCS14	G-----LMPQDYIQYTVPLDEGMYPLEGSR-----
	mSOCS17	-----RKD-----GYVWSGKK-LWSKKSESCSESEAKKG-----
	hSOCS18	GATPGTRLARRDSYSRHPWGGKKKHCSTKTQSSLDTEKKFGRTRSGLQ
40	hSOCS19	-----PSRKGSPFKIRLSRLFRTKSCNGSGG-----
	mCIS	MVLCVQG
	hSOCS1	
	mSOCS1	
45	hSOCS2	----GCTASGYFVPAARA-PAAGDQWVT--AAARDFVIR--FPGSGEKE
	hSOCS3	
	mSOCS3	
	hSOCS14	----YCLDSSSPMEVSAPVPPQVGGRAFFEDSQVDQDLVVAPEIFVDQS
	mSOCS17	---QLSCSSIELDLDHSCG-HRFLGRSLK--QKLQDAVGQCFPIKNCSGR
50	hSOCS18	RRRRRYGVSSMQDMDSVSS-RAVGSRSLR--QRLQDTVGLCFPMRTYSKQ
	hSOCS19	----GDGTGKRPSGELAAS-AASLTDMG--SAGRELDAGRKPLTRTQS

Table 1 (continued):

	mCIS	SCPLLAVEQIGRR-PLWAQSLELPGPA-----MQPLPTGA---
	hSOCs1	MVAHQVAADN-----AVSTAAEPR-----
5	msOCs1	MVARNQVAADN-----AISPAAEPR-----
	hSOCs2	PHFSLCHHFGHPAGLVLFALTERRD-----ANPSLTPARAAT---
	hSOCs3	MVTHSKFPAAG-----MSRPLDTSL-----
	msOCs3	MVTHSKFPAAC-----MSRPLDTSL-----
	hSOCs14	VNGLLIGTTGVMLQSPRAGHDVPPLS-----PLLPMQNNQ---
10	msOCs17	HSPGLPSKRRIHISELMLDXCFPPRSDLAFRWHFKRHTVPMSPNS--
	hSOCs18	SKPLFSNKRRIHISELMLKCPFPAGSDLAQKWHLIKQHTAPVSPHSTFF
	hSOCs19	AFSPVFSPLFTGETVSLVDVDSIQRG-----LTSFPHPTP---
15	mCIS	-----RRPE-----PSSSSSSS-----PAA
	hSOCs1	-----RRSE-----PSSSSSSS-----PAA
	msOCs1	-----CLCRGD-----PS-----LMTLR
	hSOCs2	-----R-----
	hSOCs3	-----R-----
20	msOCs3	-----R-----
	hSOCs14	-----IQRNFS-----GLT
	msOCs17	----DEWVSADLSERKLRLDAQLKRNTEDDIPCFSHNGQPCVITANSAS
	hSOCs18	DTFDPPLVSTDEEDRLRERRRLSIEGVDPPPNAQIHTFEATAQVNLFL
	hSOCs19	-----PPPPRRSLSLDDISGTLPTSVLVAPMGSSLSQSFPLP
25	mCIS	-PPEEVTEETPVQAENE-----PKVLDP-----
	hSOCs1	PARPRPCPAVPAPAPGD-----THFRTRFS-----
	msOCs1	PVRPRPCPAVPAPAPGD-----THFRTRFS-----
30	hSOCs2	CLEPSGNGGEGTRSPWG-----TAGSAEEP-----
	hSOCs3	-----LKTFS-----
	msOCs3	-----LKTFS-----
	hSOCs14	GTEAHVAESMRCHLNFD-----PNSAPGVARVYDSVQ-----
	msOCs17	CTGGHITGSMNLTNN--SIEDSDMSEDEIITLCTSSRKRKNPR--WEM
35	hSOCs18	KLGPKLAPGMTETSGDSSAIPQANCSEEDTTLCQSR--RQQRQISGD
	hSOCs19	PPPPPHAPDAFPRIAPR-----AASLHSQPP-----
40	mCIS	-----EGDLLCIAKTFSYLRES--GWYWSITASEARQHLQ
	hSOCs1	-----HADYRRITRASALLDAC--GFYWGPLSVHGAHERLR
	msOCs1	-----HSDYRRITRTSALLDAC--GFYWGPLSVHGAHERLR
	hSOCs2	-----SPQAARLAKALRELQGT--GWYWSMTVNEAKEKLK
	hSOCs3	-----KSEYQLVNVNAVRKLQES--GFYWSAVTGGEANLLS
	msOCs3	-----KSEYQLVNVNAVRKLQES--GFYWSAVTGGEANLLS
45	hSOCs14	-----SSGPMVVTSLTEELKKLAKQGWYWGPIRWEAEGKLA
	msOCs17	EEIILQLEAPPKFHTQIDYVHCLVPDLLQISNNPCYWGVMKDYAAEALLE
	hSOCs18	SHTHVSRQGAWKVHTQIDYIHCLVPDLLQITGNPCYWGMDRYEAALSE
	hSOCs19	----QHLQCPLYRPDSSFAASLRELEKC--GWYWGPMNWEAEMKLE

* ** *

Table 1 (continued):

5	mCIS	KMPEGTFLVRDST-HPSYFLTSLVKTTTRGPTNVRIEYADSSFRLDNSNCLS
	hSOCs1	AEPVGTFLVRDSR-QRNCFFALSVMKASGPTSI RVHFQAGRFLHDGS-R-
	msOCs1	AEPVGTFLVRDSR-QRNCFFALSVMKASGPTSI RVHFQAGRFLHDGS-R-
	hSOCs2	EAPEGTFLIRDSS-HSDYLLTISVKTSGPTNLRIEQDGKFRLDSTICV
	hSOCs3	AEPAGTFLIRDSSDQR-HFFALS VKTSGTKNLRIQCEGGSFSLQSDPRS
10	msOCs3	AEPAGTFLIRDSSDQR-HFFTSLSVKTSQGTKNLRIQCEGGSFSLQSDPRS
	hSOCs14	NVPDGSFLVRDSS-DDRYLLSLSFRRSHGKTLHTRI EHSNGRFSFYEQPD-
	msOCs17	GKPEGTFLLRDSA-QEDYLFVSFRYSRSLHARIEQWNHNSFSDAHPD-
	hSOCs18	GKPEGTFLLRDSA-QEDYLFVSSSAATTGSLHARIEQWNHNSFSDAHPD-
	hSOCs19	GKPDGSFLVRDSS-DPRYLLSLSFRRSQGITHHTRMEHYRGTFSLWCHPKF * * . * . * . * . * . * . *
15	mCIS	RP-RILAFPDDVSLVQHYVASCADTRSDSPDPAPTALPMSKQDAPSDS
	hSOCs1	-----ESFDCLFELLEHYVAAF-----RRMLG
	msOCs1	-----ETFDCLFELLEHYVAAF-----RRMLG
	hSOCs2	KS-KLKQDFSVVHLIDYYVQCMCKD-----RTGPEAPRNG
	hSOCs3	TQ-PVPRFDCVLKLVHYHMPGPAPSPF-SPTPEPSSEVPQPSAQPLPG
20	msOCs3	TQ-PVPRFDCVLKLVHYHMPGPPTFSFS-LPPTPEPSSEVPQPSAQALPG
	hSOCs14	----VERTYSIVDLIEHSIQGLENG-----AFCYSRSLRPGSA
	msOCs17	---CVFHSPTDITGLLEHYKDPSS-----CMFFEPLLS
	hSOCs18	---CVFHSSTVTGLLEHYKDPSS-----CMFFEPLLT
	hSOCs19	EDRCQSVVEFIKRAIMHSHKNGK-----FLYFLRSRVVPLGP
25	mCIS	VLPPIPVATAVHLKLVQPPVRRSS---ARSLQHLCLRLVINRLVA---DVD
	hSOCs1	-----APLRQRR-----VRPLQELCRQRIVATVG-RENLA
	msOCs1	-----APLRQRR-----VRPLQELCRQRIVAAVG-RENLA
	hSOCs2	-----TVHLYLTKPLYTSAPSLQHLCLRLTINKCTG---AIW
	hSOCs3	SPRRAYYYISGGEKI PLVLSRPLSSNVATLQHLCKRTVNGHLDSEYKVT
30	msOCs3	STPKRAYYYISGGEKI PLVLSRPLSSNVATLQHLCKRTVNGHLDSEYKVT
	hSOCs14	TYP-----VRLTNPVSRFMQVRSIQYLCRFVIRQYTR-IDLIQ
	msOCs17	-----TPLIRTFP-----FSLQHCIRCTVICNCTT-YDGID
	hSOCs18	-----ISLNRTPF-----FSLQYICRAVICRCTT-YDGID
	hSOCs19	PTP-----VQLLYPVSRFSNVKSLQHLCLCRFIRIQLVR-IDHI P * * . * . * . *
40	mCIS	CLPLPRMADYLRQYPPQL
	hSOCs1	RIPLNPVLRDYLSSFPFQI
	msOCs1	RIPLNPVLRDYLSSFPFQI
	hSOCs2	GLPLPTRLKDYLEEYKPVQ
	hSOCs3	QLPG-P-IREFLDQYDAPL
45	msOCs3	QLPG-P-IREFLDQYDAPL
	hSOCs14	KLPLPNMKDYLQEKHY
	msOCs17	ALPIPSMKLYLKEVHYKSKVRLLRIDVPEQQ
	hSOCs18	GLPLPSMLQDFLKEVHYKQKVRVRLERPEPVAK
	hSOCs19	DLPLPKPLISYIRKFYYDDPQEEVYLSLKEAQLISKQKQVEPEST * * . * . * . *

WHAT IS CLAIMED IS:

1. An isolated or recombinant polypeptide comprising:
 - a) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 2 or 6;
 - b) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 4 or 8;
 - c) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 10;
 - d) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 12;
 - e) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 14; or
 - f) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 16.
2. The polypeptide of claim 1, comprising the amino acid sequence of:
 - a) a SOCS14 of SEQ ID NO: 2 or 6;
 - b) a SOCS15 (WDS11) of SEQ ID NO: 4 or 8;
 - c) a SOCS17 of SEQ ID NO: 10;
 - d) a SOCS18 of SEQ ID NO: 12;
 - e) a SOCS19 of SEQ ID NO: 14; or
 - f) a WDS12 of SEQ ID NO: 16.
3. A fusion protein comprising the polypeptide of claim 1 or 2.
4. A binding compound which specifically binds to the polypeptide of claim 1 or 2.
5. The binding compound of claim 4 which is an antibody or antibody fragment.
6. A nucleic acid encoding the polypeptide of claim 1 or 2.
7. An expression vector comprising the nucleic acid of claim 6.
8. A host cell comprising the vector of claim 7.
9. A process for recombinantly producing a polypeptide comprising culturing the host cell of claim 8 under conditions in which the polypeptide is expressed.

SEQUENCE LISTING

SEQ ID NO: 1 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 2 is primate SOCS14 amino acid sequence.
5 SEQ ID NO: 3 is rodent SOCS15 (WDS11) nucleic acid sequence.
SEQ ID NO: 4 is rodent SOCS15 (WDS11) amino acid sequence.
SEQ ID NO: 5 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 6 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 7 is primate SOCS15 (WDS11) amino acid sequence.
10 SEQ ID NO: 8 is primate SOCS15 (WDS11) nucleic acid sequence.
SEQ ID NO: 9 is rodent SOCS17 amino acid sequence.
SEQ ID NO: 10 is rodent SOCS17 nucleic acid sequence.
SEQ ID NO: 11 is primate SOCS18 amino acid sequence.
SEQ ID NO: 12 is primate SOCS18 nucleic acid sequence.
15 SEQ ID NO: 13 is primate SOCS19 nucleic acid sequence.
SEQ ID NO: 14 is primate SOCS19 amino acid sequence.
SEQ ID NO: 15 is primate WDS12 nucleic acid sequence.
SEQ ID NO: 16 is mouse WDS12 amino acid sequence.
SEQ ID NO: 17 is mouse CIS amino acid sequence.
20 SEQ ID NO: 18 is primate SOCS1 amino acid sequence.
SEQ ID NO: 19 is murine SOCS1 amino acid sequence.
SEQ ID NO: 20 is primate SOCS2 amino acid sequence.
SEQ ID NO: 21 is primate SOCS3 amino acid sequence.
SEQ ID NO: 22 is murine SOCS3 amino acid sequence.
25 SEQ ID NO: 23 is primate SOCS16 amino acid sequence.
SEQ ID NO: 24 is primate SOCS14 nucleotide sequence.
SEQ ID NO: 25 is primate SOCS15 (WDS11) nucleotide sequence.
SEQ ID NO: 26 is rodent SOCS17 nucleotide sequence.
SEQ ID NO: 27 is primate SOCS18 nucleotide sequence.
30 SEQ ID NO: 28 is primate SOCS19 nucleotide sequence.
SEQ ID NO: 29 is primate WDS12 nucleotide sequence.

(1) GENERAL INFORMATION:

35

(i) APPLICANT:

(A) NAME: Schering Corporation
(B) STREET: 2000 Galloping Hill Road
(C) CITY: Kenilworth
40 (D) STATE: New Jersey
(E) COUNTRY: USA
(F) POSTAL CODE: 07033-0530

(ii) TITLE OF INVENTION: Suppressors of Cytokine Signaling;
45 Related Reagents

(iii) NUMBER OF SEQUENCES: 29

(iv) COMPUTER READABLE FORM:

50 (A) MEDIUM TYPE: Diskette
(B) COMPUTER: Apple Macintosh
(C) OPERATING SYSTEM: Macintosh 8.0.1
(D) SOFTWARE: Microsoft Word 6.0

55 (v) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US
(B) FILING DATE: 17-JUL-1998
(C) CLASSIFICATION:

(vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/055,804
 (B) FILING DATE: 15-AUG-1997

5 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/055,853
 (B) FILING DATE: 15-AUG-1997

10 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/053,153
 (B) FILING DATE: 18-JUL-1997

15 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/053,244
 (B) FILING DATE: 18-JUL-1997

(2) INFORMATION FOR SEQ ID NO:1:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 930 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

30 (ix) FEATURE:
 (A) NAME/KEY: unsure
 (B) LOCATION: 824
 (D) OTHER INFORMATION: /note= "position 824 is ambiguous;
 may be A, C, G, or T; all code for proline"

35 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 3..929

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AC GAC CTC CAG TCT GAG ACC ACG TGC CAG GAG CAA GCC AAT TCA CTG	47
Asp Leu Gln Ser Glu Thr Thr Cys Gln Glu Gln Ala Asn Ser Leu	
1 5 10 15	
AAG AGC TCG GCT TCT CAT AAT GGA GAC CTG CAT CTT CAC CTG GAT GAA	95
Lys Ser Ser Ala Ser His Asn Gly Asp Leu His Leu His Leu Asp Glu	
20 25 30	
CAT GTG CCT GTC GTT ATT GGA CTT ATG CCT CAG GAC TAC ATT CAG TAT	143
His Val Pro Val Val Ile Gly Leu Met Pro Gln Asp Tyr Ile Gln Tyr	
35 40 45	
ACT GTG CCT TTA GAT GAG GGG ATG TAT CCT TTG GAA GGA TCA CGG AGC	191
Thr Val Pro Leu Asp Glu Gly Met Tyr Pro Leu Glu Gly Ser Arg Ser	
50 55 60	
TAT TGT CTG GAC AGC TCT TCT CCC ATG GAA GTC TCT GCG GTT CCT CCT	239
Tyr Cys Leu Asp Ser Ser Ser Pro Met Glu Val Ser Ala Val Pro Pro	
65 70 75	
CAA GTG GGA GGG CGC GCT TTC CCC GAG GAT GAG AGT CAG GTA GAC CAG	287
Gln Val Gly Gly Arg Ala Phe Pro Glu Asp Glu Ser Gln Val Asp Gln	

	80	85	90	95	
	GAC CTA GTT GTC GCC CCA GAG ATC TTC GTG GAT CAG TCC GGT GAA TGG				335
5	Asp Leu Val Val Ala 100	Pro Glu Ile Phe Val Asp Gln Ser Gly Glu Trp 110			
	CTT GTT GAT TGG CAC CAC GGG AGT CAT GTT GCA GAA CCC CGG AGA GCG				383
	Leu Val Asp Trp His His Gly Ser His Val Ala Glu Pro Arg Arg Ala 125				
10	GGT TCA CGA TGG ATG TCC CTC CAA TCT TCA CCA TTG GTT ACC TCC AAT				431
	Gly Ser Arg Trp Met Ser Leu Gln Ser Ser Pro Leu Val Thr Ser Asn 130 135 140				
15	GCA GGA ATA ATC CAA ATC CCA AAG GGG ACC TTC AGT GGA CTC ACT GGG				479
	Ala Gly Ile Ile Gln Ile Pro Lys Gly Thr Phe Ser Gly Leu Thr Gly 145 150 155				
20	ACA GAA GCC CAC GTG GCT GAA AGT ATG CGC TGT CAT TTG AAT TTT GAT				527
	Thr Glu Ala His Val Ala Glu Ser Met Arg Cys His Leu Asn Phe Asp 160 165 170 175				
	CCG AAC TCT GCT CCT GGG GTT GCA AGA GTT TAT GAC TCA GTG CAA AGT				575
25	Pro Asn Ser Ala Pro Gly Val Ala Arg Val Tyr Asp Ser Val Gln Ser 180 185 190				
	AGT GGT CCC ATG GTT GTG ACA AGC CTT ACA GAG GAG CTG AAA AAA CTT				623
	Ser Gly Pro Met Val Val Thr Ser Leu Thr Glu Glu Leu Lys Lys Leu 195 200 205				
30	GCA AAG CAA GGA TGS TAC TGG GGA CCA ATC ACA CGT TGG GAG GCA GAA				671
	Ala Lys Gln Gly Trp Tyr Trp Gly Pro Ile Thr Arg Trp Glu Ala Glu 210 215 220				
35	GGG AAG CTA GCA AAC GTG CCA GAT GGT TCT TTT CTT GTT CGG GAC AGT				719
	Gly Lys Leu Ala Asn Val Pro Asp Gly Ser Phe Leu Val Arg Asp Ser 225 230 235				
40	TCT GAC GAC CGT TAC CTT TTA AGC TTG AGC TTT CGC TCC CAT GGT AAA				767
	Ser Asp Asp Arg Tyr Leu Leu Ser Leu Ser Phe Arg Ser His Gly Lys 240 245 250 255				
	ACA CTT CAC ACT AGA ATT GAG CAC TCA AAT GGT AGG TTT AGC TTT TAT				815
45	Thr Leu His Thr Arg Ile Glu His Ser Asn Gly Arg Phe Ser Phe Tyr 260 265 270				
	GAA CAG CCC GAT GTG GAA GGA CAT ACG TCC ATA GTT GAT CTA ATT GGA				863
	Glu Gln Pro Asp Val Glu Gly His Thr Ser Ile Val Asp Leu Ile Gly 275 280 285				
50	GCA TTC AAT CAG GGA CTC TGA AAA TGG GAG CTT TTT GTT ATT CAA GGT				911
	Ala Phe Asn Gln Gly Leu * Lys Trp Glu Leu Phe Val Ile Gln Gly 290 295 300				
55	CTC GGC TGC CTG GAA TCT G				930
	Leu Gly Cys Leu Glu Ser 305				

60 (2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 309 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Asp Leu Gln Ser Glu Thr Thr Cys Gln Glu Gln Ala Asn Ser Leu Lys
 1 5 10 15
 10 Ser Ser Ala Ser His Asn Gly Asp Leu His Leu His Leu Asp Glu His
 20 25 30
 Val Pro Val Val Ile Gly Leu Met Pro Gln Asp Tyr Ile Gln Tyr Thr
 35 40 45
 15 Val Pro Leu Asp Glu Gly Met Tyr Pro Leu Glu Gly Ser Arg Ser Tyr
 50 55 60
 Cys Leu Asp Ser Ser Ser Pro Met Glu Val Ser Ala Val Pro Pro Gln
 65 70 75 80
 Val Gly Gly Arg Ala Phe Pro Glu Asp Glu Ser Gln Val Asp Gln Asp
 85 90 95
 25 Leu Val Val Ala Pro Glu Ile Phe Val Asp Gln Ser Gly Glu Trp Leu
 100 105 110
 Val Asp Trp His His Gly Ser His Val Ala Glu Pro Arg Arg Ala Gly
 115 120 125
 30 Ser Arg Trp Met Ser Leu Gln Ser Ser Pro Leu Val Thr Ser Asn Ala
 130 135 140
 Gly Ile Ile Gln Ile Pro Lys Gly Thr Phe Ser Gly Leu Thr Gly Thr
 145 150 155 160
 Glu Ala His Val Ala Glu Ser Met Arg Cys His Leu Asn Phe Asp Pro
 165 170 175
 40 Asn Ser Ala Pro Gly Val Ala Arg Val Tyr Asp Ser Val Gln Ser Ser
 180 185 190
 Gly Pro Met Val Val Thr Ser Leu Thr Glu Glu Leu Lys Lys Leu Ala
 195 200 205
 45 Lys Gln Gly Trp Tyr Trp Gly Pro Ile Thr Arg Trp Glu Ala Glu Gly
 210 215 220
 Lys Leu Ala Asn Val Pro Asp Gly Ser Phe Leu Val Arg Asp Ser Ser
 225 230 235 240
 50 Asp Asp Arg Tyr Leu Leu Ser Leu Ser Phe Arg Ser His Gly Lys Thr
 245 250 255
 55 Leu His Thr Arg Ile Glu His Ser Asn Gly Arg Phe Ser Phe Tyr Glu
 260 265 270
 Gln Pro Asp Val Glu Gly His Thr Ser Ile Val Asp Leu Ile Gly Ala
 275 280 285
 60 Phe Asn Gln Gly Leu * Lys Trp Glu Leu Phe Val Ile Gln Gly Leu
 290 295 300
 Gly Cys Leu Glu Ser

305

(2) INFORMATION FOR SEQ ID NO:3:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 476 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: cDNA

- 15 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 3..476

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

20 CA GCT TCG TAT GAC ACC AGT GTG ATT ATG TGG GAC CCC TAC ACC GGC 47
 Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly
 1 5 10 15

25 GAG AGG CTG AGG TCA CTT CAT CAC ACA CAG CTT GAA CCC ACC ATG GAT 95
 Glu Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp
 20 25 30

30 GAC AGT GAC GTC CAC ATG AGC TCC CTG AGG TCC GTG TGC TTC TCA CCT 143
 Asp Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro
 35 40 45

35 GAA GGC TTG TAT CTC GCT ACG GTG GCA GAT GAC AGG CTG CTC AGG ATC 191
 Glu Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile
 50 55 60

40 TGG GCT CTG GAA CTG AAG GCT CCG GTT GCC TTT GCT CCG ATG ACC AAT 239
 Trp Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn
 65 70 75

45 GGT CTT TGC TGC ACG TTC TTC CCA CAC GGT GGA ATT ATT GCC ACA GGG 287
 Gly Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly
 80 85 90 95

45 ACG AGA GAT GGC CAT GTC CAG TTC TGG ACA GCT CCC CGG GTC CTG TCC 335
 Thr Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser
 100 105 110

50 TCA CTG AAG CAC TTA TGC AGG AAA GCC CTC CGA AGT TTC CTG ACA ACG 383
 Ser Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr
 115 120 125

55 TAT CAA GTC CTA GCA CTG CCA ATC CCC AAG AAG ATG AAA GAG TTC CTC 431
 Tyr Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu
 130 135 140

60 ACA TAC AGG ACT TTC TAG CAG TGC CGG CTC CCC CAC CTC CTG CAG 476
 Thr Tyr Val Arg Thr Phe * Gln Cys Arg Leu Pro His Leu Leu Gln
 145 150 155

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 158 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

10 Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu
    1      5      10      15
    Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp
        20      25      30
15 Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu
    35      40      45
    Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp
    50      55      60
20 Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn Gly
    65      70      75      80
    Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr
    85      90      95
    Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser
    100     105     110
30 Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr
    115     120     125
    Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr
    130     135     140
35 Tyr Arg Thr Phe * Gln Cys Arg Leu Pro His Leu Leu Gln
    145     150     155

```

(2) INFORMATION FOR SEQ ID NO:5:

40

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2093 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

45

(ii) MOLECULE TYPE: cDNA

50

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 87..1241

55

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 20
 (D) OTHER INFORMATION: /note= "nucleotide may be A or C at
 positions: 20, 36, 1583, 1675, 1689, 1693, 1710, 1711, 1719,
 1720, 1728, 1753, 1787, and 1806."

60

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 35
 (D) OTHER INFORMATION: /note= "nucleotide may be G or T at

postions: 35, 1541, 1594, 1689, 1778, 1779, 1825, 1844, 1845,
1853, 1854, 1865, 1884, and 1893."

5 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 70
(D) OTHER INFORMATION: /note= "Nucleotide may be A or G at
positions: 70, 1461, 1630, 1677, 1713, 1725, 1734, 1735, 1757,
10 1805, 1810, and 1863."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 64
(D) OTHER INFORMATION: /note= "Nucleotide may be A or T at
15 positions: 64, 1692, 1715, 1718, 1721, 1722, 1799, 1837, 1841,
1876, and 1894."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1661
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at
20 positions: 1661, 1729, 1749, 1750, 1754, 1776, 1802, 1826, 1847,
1859, 1860, 1904, 1907, and 1911."

25 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1731
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at
positions: 1731, 1817, 1887, and 1908."

30 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1869
(D) OTHER INFORMATION: /note= "Nucleotide may be C, G, or
35 T at positions: 1869, 1883, 1885, 1886, and 1895."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1888
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or
40 G at positions: 1888, and 1896."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1877
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or
45 T at positions: 1877, and 1898."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1855
(D) OTHER INFORMATION: /note= "Nucleotide may be A, G, or
50 T at position 1855."

55 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1935
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, G,
or T at positions: 1935, and 2034."

60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TAAGGTCCAC GTCGCTCCGC AGCCATCACT ACAGGCCCGC GCCGTGGCCT CTGCGGCCCA

60

	CAATCTCCGA	GGGACCTGC	ATCAAG	ATG	GAG	GTG	AGA	GTC	AAG	GCC	TTG	GTT	113				
				Met	Glu	Val	Arg	Val	Lys	Ala	Leu	Val					
5				1				5									
	CAC	TCT	TCC	AGC	CCG	AGT	CCA	GCC	CTG	AAT	GGC	GTC	CGG	AAG	GAT	TTC	161
	His	Ser	Ser	Ser	Pro	Ser	Pro	Ala	Leu	Asn	Gly	Val	Arg	Lys	Asp	Phe	
	10					15					20					25	
10	CAC	GAC	CTC	CAG	TCT	GAG	ACC	ACG	TGC	CAG	GAG	CAA	GCC	AAT	TCA	CTG	209
	His	Asp	Leu	Gln	Ser	Glu	Thr	Thr	Cys	Gln	Glu	Gln	Ala	Asn	Ser	Leu	
					30					35						40	
	AAG	AGC	TCG	GCT	TCT	CAT	AAT	GGA	GAC	CTG	CAT	CTT	CAC	CTG	GAT	GAA	257
15	Lys	Ser	Ser	Ala	Ser	His	Asn	Gly	Asp	Leu	His	Leu	His	Leu	Asp	Glu	
				45					50					55			
	CAT	GTG	CCT	GTC	GTT	ATT	GGA	CTT	ATG	CCT	CAG	GAC	TAC	ATT	CAG	TAT	305
20	His	Val	Pro	Val	Val	Ile	Gly	Leu	Met	Pro	Gln	Asp	Tyr	Ile	Gln	Tyr	
				60				65						70			
	ACT	GTG	CCT	TTA	GAT	GAG	GGG	ATG	TAT	CCT	TTG	GAA	GGA	TCA	CGG	AGC	353
	Thr	Val	Pro	Leu	Asp	Glu	Gly	Met	Tyr	Pro	Leu	Glu	Gly	Ser	Arg	Ser	
				75			80						85				
25	TAT	TGT	CTG	GAC	AGC	TCT	TCT	CCC	ATG	GAA	GTC	TCT	CGC	GTT	CCT	CCT	401
	Tyr	Cys	Leu	Asp	Ser	Ser	Ser	Pro	Met	Glu	Val	Ser	Ala	Val	Pro	Pro	
	90					95				100					105		
30	CAA	GTG	GGA	GGG	CGC	GCT	TTC	CCC	GAG	GAT	GAG	AGT	CAG	GTA	GAC	CAG	449
	Gln	Val	Gly	Gly	Arg	Ala	Phe	Pro	Glu	Asp	Glu	Ser	Gln	Val	Asp	Gln	
					110				115						120		
	GAC	CTA	GTT	GTC	GCC	CCA	GAG	ATC	TTC	GTG	GAT	CAG	TCC	GTG	AAT	GGC	497
35	Asp	Leu	Val	Val	Ala	Pro	Glu	Ile	Phe	Val	Asp	Gln	Ser	Val	Asn	Gly	
					125				130					135			
	TTG	TTG	ATT	GGC	ACC	ACG	GGA	GTC	ATG	TTG	CAG	AGC	CCG	AGA	CGC	GGT	545
40	Leu	Leu	Ile	Gly	Thr	Thr	Gly	Val	Met	Leu	Gln	Ser	Pro	Arg	Ala	Gly	
				140				145					150				
	CAC	GAT	GAT	GTC	CCT	CCA	CTC	TCA	CCA	TTG	CTA	CCT	CCA	ATG	CAG	AAT	593
	His	Asp	Asp	Val	Pro	Pro	Leu	Ser	Pro	Leu	Leu	Pro	Pro	Met	Gln	Asn	
				155			160					165					
45	AAT	CAA	ATC	CAA	AGG	AAC	TTC	AGT	GGA	CTC	ACT	GGC	ACA	GAA	GCC	CAC	641
	Asn	Gln	Ile	Gln	Arg	Asn	Phe	Ser	Gly	Leu	Thr	Gly	Thr	Glu	Ala	His	
					175					180					185		
50	GTG	GCT	GAA	AGT	ATG	CGC	TGT	CAT	TTG	AAT	TTT	GAT	CCG	AAC	TCT	GCT	689
	Val	Ala	Glu	Ser	Met	Arg	Cys	His	Leu	Asn	Phe	Asp	Pro	Asn	Ser	Ala	
					190				195						200		
	CCT	GGG	GTT	GCA	AGA	GTT	TAT	GAC	TCA	GTG	CAA	AGT	AGT	GGT	CCC	ATG	737
55	Pro	Gly	Val	Ala	Arg	Val	Tyr	Asp	Ser	Val	Gln	Ser	Ser	Gly	Pro	Met	
				205					210					215			
	GTT	GTG	ACA	AGC	CTT	ACA	GAG	GAG	CTG	AAA	AAA	CTT	GCA	AAG	CAA	GGA	785
60	Val	Val	Thr	Ser	Leu	Thr	Glu	Glu	Leu	Lys	Lys	Leu	Ala	Lys	Gln	Gly	
				220				225					230				
	TGG	TAC	TGG	GGA	CCA	ATC	ACA	CGT	TGG	GAG	GCA	GAA	GGG	AAG	CTA	GCA	833
	Trp	Tyr	Trp	Gly	Pro	Ile	Thr	Arg	Trp	Glu	Ala	Glu	Gly	Lys	Leu	Ala	
				235			240					245					

	AAC GTG CCA GAT GGT TCT TTT CTT GTT CGG GAC AGT TCT GAC GAC CGT	881
	Asn Val Pro Asp Gly Ser Phe Leu Val Arg Asp Ser Ser Asp Asp Arg	
	250 255 260 265	
5	TAC CTT TTA AGC TTG AGC TTT CGC TCC CAT GGT AAA ACA CTT CAC ACT	929
	Tyr Leu Leu Ser Leu Ser Phe Arg Ser His Gly Lys Thr Leu His Thr	
	270 275 280	
10	AGA ATT GAG CAC TCA AAT GGT AGG TTT AGC TTT TAT GAA CAG CCA GAT	977
	Arg Ile Glu His Ser Asn Gly Arg Ser Phe Tyr Glu Gln Pro Asp	
	285 290 295	
15	GTG GAA AGG ACA TAC TCC ATA GTT GAT CTA ATT GAG CAT TCC ATC CAG	1025
	Val Glu Arg Thr Tyr Ser Ile Val Asp Leu Ile Glu His Ser Ile Gln	
	300 305 310	
20	GGA CTC GAA AAT GGA GCT TTT TGT TAT TCA AGG TCT CGG CTG CCT GGA	1073
	Gly Leu Glu Asn Gly Ala Phe Cys Tyr Ser Arg Ser Arg Leu Pro Gly	
	315 320 325	
25	TCT GCA ACT TAC CCC GTC AGA CTG ACC AAC CCA GTG TCC CGG TTC ATG	1121
	Ser Ala Thr Tyr Pro Val Arg Leu Thr Asn Pro Val Ser Arg Phe Met	
	330 335 340 345	
	CAG GTG CGC TCG TTG CAG TAC CTG TGT CGT TTT GTT ATA CGT CAG TAT	1169
	Gln Val Arg Ser Leu Gln Tyr Leu Cys Arg Phe Val Ile Arg Gln Tyr	
	350 355 360	
30	ACC AGA ATA GAC TTA ATT CAG AAA CTG CCT TTG CCA AAC AAA ATG AAG	1217
	Thr Arg Ile Asp Leu Ile Gln Lys Leu Pro Leu Pro Asn Lys Met Lys	
	365 370 375	
35	GAT TAT TTA CAG GAG AAG CAC TAC TGAAGATTG AGAACCTCG ATCTTGCAC	1271
	Asp Tyr Leu Gln Glu Lys His Tyr	
	380 385	
	TTGGGAATAA GAACAAGAGA TTGAAATACA GTTTACAAAC TTTCATTGCC ATCAAAATCT	1331
40	TTTGCTGCCA TAACTATTTC AGTTTTATGT GTAAAAGAGT CATCAGTTTG TTAGGGGGTG	1391
	GGGAAGTGTC AGCAAGGTGT CTTGGGTTTA TTTTGGTTCT TTAATAAAAGG GAAGTCTTGA	1451
	AGTTTTAGAA GTGTTGAATT ATGTTTCATC AATGTGCAGA ATAATCACAA TGTGAATTAT	1511
45	CAAATTCCTC TCAATGCCCC CCCCGCCCAT TCCTTTGCTG CTATCCACTG TGATTTTAT	1571
	GCATTAAAG CCCATTTCAT GTTTTTTCAA CCCTAAGTAA AGTTGAATGA AACTTAACAG	1631
50	AATGGAATTT GCTATTCTTT TTTAAATGGC CCATTTTCCA AAACAAGTGT TGAATAACCA	1691
	ACCTGTGTTG AATAAAACCC GAAATTACCA ATAACACCGG AGGTGAGTTT TTAATCTCCT	1751
55	ACCTTGAAAA GATTATTATTA GAATCGGGAA TTGACCTAAT ATTGGGTAAT TGGACGGAG	1811
	ATCTGCAACA TATTCTTTAA CAACAATTTA TTGGCCTTAA TTTGTTTCCA AAGGTGSCCT	1871
	TATTTCCTTG GGGGGGGAAA GGAGGAATTC TCGCTCCCCC TCGTTTTCAT CTTCAGTATT	1931
60	GTGCTATTTT AATAAATGGC CTTACATTAA AAAATTGTAA AGAAATGTAT ACCACCAATT	1991
	TAGAAATGTT TGCCTTTTCT GTAATTAAAC TCGGGTACAA ATCGGCATAA CATGAAAACC	2051
	TATGGAACCTA GAATTATTAT TAAAGAAATA TTAGATGATC AT	2093

(2) INFORMATION FOR SEQ ID NO:6:

5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 385 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

15 Met Glu Val Arg Val Lys Ala Leu Val His Ser Ser Ser Pro Ser Pro
 1 5 10 15
 Ala Leu Asn Gly Val Arg Lys Asp Phe His Asp Leu Gln Ser Glu Thr
 20 25 30
 Thr Cys Gln Glu Gln Ala Asn Ser Leu Lys Ser Ser Ala Ser His Asn
 35 40 45
 Gly Asp Leu His Leu His Leu Asp Glu His Val Pro Val Val Ile Gly
 50 55 60
 25 Leu Met Pro Gln Asp Tyr Ile Gln Tyr Thr Val Pro Leu Asp Glu Gly
 65 70 75 80
 Met Tyr Pro Leu Glu Gly Ser Arg Ser Tyr Cys Leu Asp Ser Ser Ser
 30 85 90 95
 Pro Met Glu Val Ser Ala Val Pro Pro Gln Val Gly Gly Arg Ala Phe
 100 105 110
 35 Pro Glu Asp Glu Ser Gln Val Asp Gln Asp Leu Val Val Ala Pro Glu
 115 120 125
 Ile Phe Val Asp Gln Ser Val Asn Gly Leu Leu Ile Gly Thr Thr Gly
 130 135 140
 40 Val Met Leu Gln Ser Pro Arg Ala Gly His Asp Asp Val Pro Pro Leu
 145 150 155 160
 Ser Pro Leu Leu Pro Pro Met Gln Asn Asn Gln Ile Gln Arg Asn Phe
 45 165 170 175
 Ser Gly Leu Thr Gly Thr Glu Ala His Val Ala Glu Ser Met Arg Cys
 180 185 190
 50 His Leu Asn Phe Asp Pro Asn Ser Ala Pro Gly Val Ala Arg Val Tyr
 195 200 205
 Asp Ser Val Gln Ser Ser Gly Pro Met Val Val Thr Ser Leu Thr Glu
 210 215 220
 55 Glu Leu Lys Lys Leu Ala Lys Gln Gly Trp Tyr Trp Gly Pro Ile Thr
 225 230 235 240
 Arg Trp Glu Ala Glu Gly Lys Leu Ala Asn Val Pro Asp Gly Ser Phe
 60 245 250 255
 Leu Val Arg Asp Ser Ser Asp Asp Arg Tyr Leu Leu Ser Leu Ser Phe
 260 265 270

Arg Ser His Gly Lys Thr Leu His Thr Arg Ile Glu His Ser Asn Gly
 275 280 285
 5 Arg Phe Ser Phe Tyr Glu Gln Pro Asp Val Glu Arg Thr Tyr Ser Ile
 290 295 300
 Val Asp Leu Ile Glu His Ser Ile Gln Gly Leu Glu Asn Gly Ala Phe
 305 310 315 320
 10 Cys Tyr Ser Arg Ser Arg Leu Pro Gly Ser Ala Thr Tyr Pro Val Arg
 325 330 335
 Leu Thr Asn Pro Val Ser Arg Phe Met Gln Val Arg Ser Leu Gln Tyr
 340 345 350
 15 Leu Cys Arg Phe Val Ile Arg Gln Tyr Thr Arg Ile Asp Leu Ile Gln
 355 360 365
 20 Lys Leu Pro Leu Pro Asn Lys Met Lys Asp Tyr Leu Gln Glu Lys His
 370 375 380
 Tyr
 385
 25 (2) INFORMATION FOR SEQ ID NO:7:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1748 base pairs
 (B) TYPE: nucleic acid
 30 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: cDNA
 35 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 1..1335
 40 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1026
 (D) OTHER INFORMATION: /note= "Nucleotide may be C or T at
 45 positions: 1026, 1032, 1041, 1452, 1510, and 1567."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 945
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or G at
 50 positions: 945, 1376, 1541, 1658, 1662, and 1668."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1435
 55 (D) OTHER INFORMATION: /note= "Nucleotide may be G or T at
 positions: 1435, 1481, 1518, and 1543."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 60 (B) LOCATION: 1500
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or C at
 positions: 1500, and 1669."
 (ix) FEATURE:

(A) NAME/KEY: misc_feature
 (B) LOCATION: 1521
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or T at positions: 1521, and 1542."

5 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1651
 10 T at position 1651."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1654
 15 C at position 1654."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1656
 20 A at position 1656."
 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1589..1649
 25 or G at positions: 1589-1649, 1652, 1655, 1657-1661, 1664-1667,
 and 1672-1748."
 30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

35	ATG GAG GCC GGA GAG GAA CCG CTG CTG CTG GCC GAA CTC AAG CCC GGG	48
	Met Glu Ala Gly Glu Glu Pro Leu Leu Leu Ala Glu Leu Lys Pro Gly	
	1 5 10 15	
40	CGC CCC CAC CAG TTT GAT TGG AAG TCC AGC TGT GAA ACC TGG AGC GTG	96
	Arg Pro His Gln Phe Asp Trp Lys Ser Ser Cys Glu Thr Trp Ser Val	
	20 25 30	
45	GCC TTC TCG CCA GAC GGT TCC TGG TTC GCC TGG TCT CAA GGA CAC TGC	144
	Ala Phe Ser Pro Asp Gly Ser Trp Phe Ala Trp Ser Gln Gly His Cys	
	35 40 45	
50	GTG GTC AAG CTG GTC CCC TGG CCC TTA GAG GAA CAG TTC ATC CCT AAA	192
	Val Val Lys Leu Val Pro Trp Pro Leu Glu Glu Gln Phe Ile Pro Lys	
	50 55 60	
55	GGA TTC GAA GCC AAG AGC CGA AGC AGC AAG AAT GAC CCA AAA GGA CGG	240
	Gly Phe Glu Ala Lys Ser Arg Ser Ser Lys Asn Asp Pro Lys Gly Arg	
	65 70 75 80	
60	GGC AGT CTG AAG GAG AAG ACG CTG GAC TGT GGC CAG ATT GTG TGG GGG	288
	Gly Ser Leu Lys Glu Lys Thr Leu Asp Cys Gly Gln Ile Val Trp Gly	
	85 90 95	
	CTG GCC TTC AGC CCA TGG CCC TCT CCA CCC AGC AGG AAA CTC TGG GCA	336
	Leu Ala Phe Ser Pro Trp Pro Ser Pro Pro Ser Arg Lys Leu Trp Ala	
	100 105 110	
	CGT CAC CAT CCC CAG GCG CCT GAT GTT TCT TGC CTG ATC CTG GCC ACA	384
	Arg His His Pro Gln Ala Pro Asp Val Ser Cys Leu Ile Leu Ala Thr	
	115 120 125	

	GGT CTC AAC GAT GGG CAG ATC AAG ATT TGG GAG GTA CAG ACA GGC CTC	432
	Gly Leu Asn Asp Gly Gln Ile Lys Ile Trp Glu Val Gln Thr Gly Leu	
	130 135 140	
5	CTG CTT CTG AAT CTT TCT GGC CAC CAA GAC GTC GTG AGA GAT CTG AGC	480
	Leu Leu Leu Asn Leu Ser Gly His Gln Asp Val Val Arg Asp Leu Ser	
	145 150 155 160	
10	TTC ACG CCC AGC GGC AGT TTG ATT TTG GTC TCT GCA TCC CGG GAT AAG	528
	Phe Thr Pro Ser Gly Ser Leu Ile Leu Val Ser Ala Ser Arg Asp Lys	
	165 170 175	
15	ACA CTT CGA ATT TGG GAC CTG AAT AAG CAC GGT AAG CAG ATC CAG GTG	576
	Thr Leu Arg Ile Trp Asp Leu Asn Lys His Gly Lys Gln Ile Gln Val	
	180 185 190	
20	TTA TCC GGC CAT CTG CAG TGG GTT TAC TGC TGC TCC ATC TCC CCT GAC	624
	Leu Ser Gly His Leu Gln Trp Val Tyr Cys Cys Ser Ile Ser Pro Asp	
	195 200 205	
	TGT AGC ATG CTG TGC TCT GCA GCT GGG GAG AAG TCG GTC TTT CTG TGG	672
	Cys Ser Met Leu Cys Ser Ala Ala Gly Glu Lys Ser Val Phe Leu Trp	
	210 215 220	
25	AGC ATG CGG TCC TAC ACA CTA ATC CGG AAA CTA GAA GGC CAC CAA AGC	720
	Ser Met Arg Ser Tyr Thr Leu Ile Arg Lys Leu Glu Gly His Gln Ser	
	225 230 235 240	
30	AGT GTT GTC TCC TGT GAT TTC TCT CCT GAT TCA GCC TTG CTT GTC ACA	768
	Ser Val Val Ser Cys Asp Phe Ser Pro Asp Ser Ala Leu Leu Val Thr	
	245 250 255	
35	GCT TCG TAT GAC ACC AGT GTG ATT ATG TGG GAC CCC TAC ACC GGC GAG	816
	Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu	
	260 265 270	
40	AGG CTG AGG TCA CTT CAT CAC ACA CAG CTT GAA CCC ACC ATG GAT GAC	864
	Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp	
	275 280 285	
	AGT GAC GTC CAC ATG AGC TCC CTG AGG TCC GTG TGC TTC TCA CCT GAA	912
	Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu	
	290 295 300	
45	GGC TTG TAT CTC GCT ACG GTG GCA GAT GAC AGA CTG CTC AGG ATC TGG	960
	Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp	
	305 310 315 320	
50	GCT CTG GAA CTG AAA GCT CCG GTT GCC TTT GCT CCG ATG ACC AAT GGT	1008
	Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asp Gly	
	325 330 335	
55	CTT TGC TGC ACA TTT TTC CCA CAC GGT GGA ATC ATT GCC ACA GGG ACA	1056
	Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr	
	340 345 350	
	AGA GAT GGC CAC GTC CAG TTC TGG ACA GCT CCT AGG GTC CTG TCC TCA	1104
	Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser	
	355 360 365	
60	CTG AAG CAC TTA TGC CGG AAA GCC CTT CGA AGT TTC CTA ACA ACT TAC	1152
	Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr	
	370 375 380	

	CAA GTC CTA GCA CTG CCA ATC CCC AAG AAA ATG AAA GAG TTC CTC ACA Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr 385 390 395 400	1200
5	TAC AGG ACT TTT TAA GCA ACA CCA CAT CTT GTG CTT CTT TGT AGC AGG Tyr Arg Thr Phe * Ala Thr Pro His Leu Val Leu Leu Cys Ser Arg 405 410 415	1248
10	GTA AAT CGT CCT GTC AAA GGG AGT TGC TGG AAT AAT GGG CCA AAC ATC Val Asn Arg Pro Val Lys Gly Ser Cys Trp Asn Asn Gly Pro Asn Ile 420 425 430	1296
15	TGG TCT TGC ATT GAA ATA GCA TTT CTT TGG GAT TGT GAA TAGAATGTAG Trp Ser Cys Ile Glu Ile Ala Phe Leu Trp Asp Cys Glu 435 440 445	1345
	CAAAACCAGA TTCCAGTGTA CTAGTCATGG GTCTTTCTCT CCCTGGGCAT GTGGAAAGTC	1405
20	AGTCTTAGGA GGAAGGAGA TTCCACTTGG CACGGGCAAC AGAGCCCTTA CGTTTAAATT TTTCAGTCCA GTTATTGAAC AGCAAGTGT TGAAATCTTT CTGGCTTGTT TTGGATTCA	1465
	AAGTGGCAGT TACTGGTGGT TGTTTTGGGA TTTATGGCAA CCAAGTTAGG GCCTCCAGCG	1525
25	GTCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCTCCACC CGGCCATCC CCACATCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC	1585
	CCCCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC	1645
30	CCCCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC	1705
	CCCCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC	1745

(2) INFORMATION FOR SEQ ID NO:8:

35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 445 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear	
40	(ii) MOLECULE TYPE: protein	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:	
45	Met Glu Ala Gly Glu Glu Pro Leu Leu Leu Ala Glu Leu Lys Pro Gly 1 5 10 15 Arg Pro His Gln Phe Asp Trp Lys Ser Ser Cys Glu Thr Trp Ser Val 20 25 30	
50	Ala Phe Ser Pro Asp Gly Ser Trp Phe Ala Trp Ser Gln Gly His Cys 35 40 45 Val Val Lys Leu Val Pro Trp Pro Leu Glu Glu Gln Phe Ile Pro Lys 50 55 60	
55	Gly Phe Glu Ala Lys Ser Arg Ser Ser Lys Asn Asp Pro Lys Gly Arg 65 70 75 80 Gly Ser Leu Lys Glu Lys Thr Leu Asp Cys Gly Gln Ile Val Trp Gly 85 90 95	
60	Leu Ala Phe Ser Pro Trp Pro Ser Pro Pro Ser Arg Lys Leu Trp Ala 100 105 110	

Arg His His Pro Gln Ala Pro Asp Val Ser Cys Leu Ile Leu Ala Thr
 115 120 125
 5 Gly Leu Asn Asp Gly Gln Ile Lys Ile Trp Glu Val Gln Thr Gly Leu
 130 135 140
 Leu Leu Leu Asn Leu Ser Gly His Gln Asp Val Val Arg Asp Leu Ser
 145 150 155 160
 10 Phe Thr Pro Ser Gly Ser Leu Ile Leu Val Ser Ala Ser Arg Asp Lys
 165 170 175
 Thr Leu Arg Ile Trp Asp Leu Asn Lys His Gly Lys Gln Ile Gln Val
 180 185 190
 15 Leu Ser Gly His Leu Gln Trp Val Tyr Cys Cys Ser Ile Ser Pro Asp
 195 200 205
 20 Cys Ser Met Leu Cys Ser Ala Ala Gly Glu Lys Ser Val Phe Leu Trp
 210 215 220
 Ser Met Arg Ser Tyr Thr Leu Ile Arg Lys Leu Glu Gly His Gln Ser
 225 230 235 240
 25 Ser Val Val Ser Cys Asp Phe Ser Pro Asp Ser Ala Leu Leu Val Thr
 245 250 255
 Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu
 260 265 270
 30 Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp
 275 280 285
 35 Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu
 290 295 300
 Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp
 305 310 315 320
 40 Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn Gly
 325 330 335
 Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr
 340 345 350
 45 Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser
 355 360 365
 50 Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr
 370 375 380
 Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr
 385 390 395 400
 55 Tyr Arg Thr Phe * Ala Thr Pro His Leu Val Leu Leu Cys Ser Arg
 405 410 415
 Val Asn Arg Pro Val Lys Gly Ser Cys Trp Asn Asn Gly Pro Asn Ile
 420 425 430
 60 Trp Ser Cys Ile Glu Ile Ala Phe Leu Trp Asp Cys Glu
 435 440 445

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2198 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1419
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1680
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at positions: 1680, 1691, 1696, 1704, 1707, 1728, 1740, 1743, 1746, 1755, 1760, 1770, 1773, 1802, 1816, 1817, 1823, 1826, 1827, 1846, 1851, 1857, 1861, 1880, and 1885."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1909
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at positions: 1909, 1917, 1920, 1929, 1946, 1953, 1967-8, 1980, 1991, 1995, 2001, 2004, 2021, 2033-37, 2039-40, 2042, 2048, 2051, 2054, 2061, 2075, 2081, and 2083-85. "
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2088
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at positions: 2088, 2105, 2121, 2124, 2132, 2137, 2147, 2149, 2151-52, 2160, 2165, 2177, 2179 and 2196."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 494
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at position 494."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 498
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at positions: 498, 501, 1455, 1524, 1527, 1621, 1829, and 2072."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 499
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at positions: 499, 1618, and 1664."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1673
(D) OTHER INFORMATION: /note= "Nucleotide may be G or T at position 1673."
- (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1819

	225		230		235		240	
	GGT GGT CAC ATA ACT GGT TCT ATG ATG AAC TTG GTC ACA AAC AAC AGC							768
5	Gly Gly His Ile Thr Gly Ser Met Met Asn Leu Val Thr Asn Asn Ser		245		250		255	
	ATA GAA GAC AGT GAC ATG GAT TCA GAG GAT GAA ATT ATA ACG CTG TGC							816
10	Ile Glu Asp Ser Asp Met Asp Ser Glu Asp Glu Ile Ile Thr Leu Cys		260		265		270	
	ACA AGC TCC AGA AAA AGG AAT AAG CCC AGG TGG GAA ATG GAA GAG GAG							864
	Thr Ser Ser Arg Lys Arg Asn Lys Pro Arg Trp Glu Met Glu Glu Glu		275		280		285	
15	ATC CTG CAG TTG GAG GCA CCT CCT AAG TTC CAC ACC CAG ATC GAC TAC							912
	Ile Leu Gln Leu Glu Ala Pro Pro Lys Phe His Thr Gln Ile Asp Tyr		290		295		300	
20	GTC CAC TGC CTT GTT CCA GAC CTC CTT CAG ATC AGT AAC AAT CCG TGC							960
	Val His Cys Leu Val Pro Asp Leu Leu Gln Ile Ser Asn Asn Pro Cys		305		310		315	
	TAC TGG GGT GTC ATG GAC AAA TAT GCA GCC GAA GCT CTG CTG GAA GGA							1008
25	Tyr Trp Gly Val Met Asp Lys Tyr Ala Ala Glu Ala Leu Leu Glu Gly		325		330		335	
	AAG CCA GAG GGC ACC TTT TTA CTT CGA GAT TCA GCG CAG GAA GAT TAT							1056
30	Lys Pro Glu Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr		340		345		350	
	TTA TTC TCT GTT AGT TTT AGA CGC TAC AGT CGT TCT CTT CAT GCT AGA							1104
	Leu Phe Ser Val Ser Phe Arg Arg Tyr Ser Arg Ser Leu His Ala Arg		355		360		365	
35	ATT GAG CAG TGG AAT CAT AAC TTT AGC TTT GAT GCC CAT GAT CCT TGT							1152
	Ile Glu Gln Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys		370		375		380	
40	GTC TTC CAT TCT CCT GAT ATT ACT GGG CTC CTG GAA CAC TAT AAG GAC							1200
	Val Phe His Ser Pro Asp Ile Thr Gly Leu Leu Glu His Tyr Lys Asp		385		390		395	
	CCC AGT GCC TGT ATG TTC TTT GAG CCG CTC TTG TCC ACT CCC TTA ATC							1248
45	Pro Ser Ala Cys Met Phe Phe Glu Pro Leu Leu Ser Thr Pro Leu Ile		405		410		415	
	CGG ACG TTC CCC TTT TCC TTG CAG CAT ATT TGC AGA ACG GTT ATT TGT							1296
50	Arg Thr Phe Pro Phe Ser Leu Gln His Ile Cys Arg Thr Val Ile Cys		420		425		430	
	AAT TGT ACG ACT TAC GAT GGC ATC GAT GCC CTT CCC ATT CCT TCG CCT							1344
	Asn Cys Thr Thr Tyr Asp Gly Ile Asp Ala Leu Pro Ile Pro Ser Pro		435		440		445	
55	ATG AAA TTG TAT CTG AAG GAA TAC CAT TAT AAA TCA AAA GTT AGG TTA							1392
	Met Lys Leu Tyr Leu Lys Glu Tyr His Tyr Lys Ser Lys Val Arg Leu		450		455		460	
60	CTC AGG ATT GAT GTG CCA GAG CAG CAG TGATGCGGAG AGGTTAGAAT							1439
	Leu Arg Ile Asp Val Pro Glu Gln Gln		465		470			
	GTCCACCGGA GCTTTTGTTT CCTTTAGTGA GGGTTAATTT CGAGCTTGGC GTAATCATGG							1499

TCATAGCTGT TTCCTGTGTG AAATTGTAT CCGCTCACAA TTCCACACAA CATACGAGCC 1559
 GGAAGCATAA AGTGTAAAGC CTGGGGTGCC TAATGAGTGA GCTAACTCAC ATTAATTGGG 1619
 5 TCGCCTCAC TGCCTGCTTT CCAGTCGGA AACCTGCTGT GCCAGCTGCA TTAAGAATC 1679
 CGCAACTCG CCGGGACAGC GGTTAGCCTA TTGGGCGCTC TTAAGTCTC CGCTCACTGA 1739
 10 CTCCCTCCCT CGGTCTTTCG CTGCTGCTAC CGTCTCCCC ATCCAAGCGT TATACGCTAT 1799
 CCCCAGAACT GGGAAACCCC GAACACCCTC ACAAAGCTCA CTGCTACCGT ACACGCCCTG 1859
 CCGGCTTTTC CTCGTCCCC CACACCCTAA ACAGCCCTCG AGTGCAACCC CGATATACAT 1919
 15 CTCTTCCCTC AACCCCTGCC TCTGTCCCCG CCTCCGACTT CGCTTCCCGG GATTGCTTTC 1979
 CCCCCGTAGT CCGTCTAGT GCGCGCGGCC TTCCACCCTT CCACCCTTAC GTACCCCCAC 2039
 20 CCCCCAAACC CCCCCCCCCC CCGATAAAAA GTACGCGCCT TCACCCCCC GATAAAAAATG 2099
 GTCCCTACT TTCCAATGTC TCCCCCCCG CTCTTCTCGC CACCCAACCT ACCTTTCCGG 2159
 CACTGCATCC GGTGCTACCC TCCTGTTTCT CCTCCCCC 2198

25

(2) INFORMATION FOR SEQ ID NO:10:

30

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 473 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gly Gly Gly Asp Gly Gly Arg Arg Ser Asp Ser Ser Ala * Ala Glu
 1 5 10 15
 40 Leu Gly Glu Ile Arg Pro Glu Ser Ala Gln Lys Lys Leu Pro Leu Arg
 20 25 30
 Lys Ala Glu Asn Thr Ile Phe Ile Thr Leu Glu Ile Val Lys Asn Leu
 35 40 45
 45 Phe Lys Met Ala Glu Asn Asn Ser Lys Asn Val Asp Val Arg Pro Lys
 50 55 60
 Thr Ser Arg Ser Arg Ser Ala Asp Arg Lys Asp Gly Tyr Val Trp Ser
 50 65 70 75 80
 Gly Lys Lys Leu Ser Trp Ser Lys Lys Ser Glu Ser Cys Ser Glu Ser
 85 90 95
 55 Glu Ala Lys Lys Gly Gln Leu Ser Cys Ser Ser Ile Glu Leu Asp Leu
 100 105 110
 Asp His Ser Cys Gly His Arg Phe Leu Gly Arg Ser Leu Lys Gln Lys
 115 120 125
 60 Leu Gln Asp Ala Val Gly Gln Cys Phe Pro Ile Lys Asn Cys Ser Gly
 130 135 140
 Arg His Ser Pro Gly Leu Pro Ser Lys Arg Lys Ile His Ile Ser Glu

	145		150		155		160
	Leu Met Leu Asp	Thr Cys Pro Phe	Pro Pro Arg Ser Asp	Leu Ala Phe			
		165		170		175	
5	Arg Trp His Phe	Ile Lys Arg His	Thr Val Pro Met Ser	Pro Asn Ser			
		180		185		190	
10	Asp Glu Trp Val	Ser Ala Asp Leu	Ser Glu Arg Lys	Leu Arg Asp Ala			
		195		200		205	
	Gln Leu Lys Arg	Arg Asn Thr Glu	Asp Asp Ile Pro	Cys Phe Ser His			
		210		215		220	
15	Thr Asn Gly Gln	Pro Cys Val Ile	Thr Ala Asn Ser	Ala Ser Cys Thr			
		225		230		235	
	Gly Gly His Ile	Thr Gly Ser Met	Met Asn Leu Val	Thr Asn Asn Ser			
		245		250		255	
20	Ile Glu Asp Ser	Asp Met Asp Ser	Glu Asp Glu Ile	Ile Ile Thr Leu Cys			
		260		265		270	
25	Thr Ser Ser Arg	Lys Arg Asn Lys	Pro Arg Trp Glu	Met Glu Glu Glu			
		275		280		285	
	Ile Leu Gln Leu	Glu Ala Pro Pro	Lys Phe His Thr	Gln Ile Asp Tyr			
		290		295		300	
30	Val His Cys Leu	Val Pro Asp Leu	Leu Gln Ile Ser	Asn Asn Pro Cys			
		305		310		315	
	Tyr Trp Gly Val	Met Asp Lys Tyr	Ala Ala Glu Ala	Leu Leu Glu Gly			
		325		330		335	
35	Lys Pro Glu Gly	Thr Phe Leu Leu	Arg Asp Ser Ala	Gln Glu Asp Tyr			
		340		345		350	
40	Leu Phe Ser Val	Ser Phe Arg Arg	Tyr Ser Arg Ser	Leu His Ala Arg			
		355		360		365	
	Ile Glu Gln Trp	Asn His Asn Phe	Ser Phe Asp Ala	His Asp Pro Cys			
		370		375		380	
45	Val Phe His Ser	Pro Asp Ile Thr	Gly Leu Leu Glu	His Tyr Lys Asp			
		385		390		395	
	Pro Ser Ala Cys	Met Phe Phe Glu	Pro Leu Leu Ser	Thr Pro Leu Ile			
		405		410		415	
50	Arg Thr Phe Pro	Phe Ser Leu Gln	His Ile Cys Arg	Thr Val Ile Cys			
		420		425		430	
55	Asn Cys Thr Thr	Tyr Asp Gly Ile	Asp Ala Leu Pro	Ile Pro Ser Pro			
		435		440		445	
	Met Lys Leu Tyr	Leu Lys Glu Tyr	His Tyr Lys Ser	Lys Val Arg Leu			
		450		455		460	
60	Leu Arg Ile Asp	Val Pro Glu Gln	Gln				
		465		470			

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2254 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 117..1724

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 740
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or C at positions: 740, 797, 2139, and 2184."

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 761
 (D) OTHER INFORMATION: /note= "Nucleotide may be G or T at positions: 761, 1313, 1508, and 2226."

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 746
 (D) OTHER INFORMATION: /note= "Nucleotide may be C or T at positions 746, 1460, 1499, 2009, 2010, 2199, and 2225. "

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 788
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or G at positions 788, 863, 1550, 2178, 2188, 2197, and 2211."

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1163
 (D) OTHER INFORMATION: /note= "Nucleotide may be G or C at positions: 1163, and 1544."

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 2058
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or T at positions 2058, and 2128."

(ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 2251
 (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at position 2251."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CTCGGGCCGG GATGGATCCG CCGGAAGAG GAAGACAAGC GGAGCGTTGA GCCCTGCGC 60

ACGGTGCCCC GCGCGTAGTG GGAGCTTACT CGCAGTAGCT CTCGCTCTTC TAATCA 116

ATG GAT AAA GTG GGG AAA ATG TGG AAC AAC TTA AAA TAC AGA TGC CAG 164

Met Asp Lys Val Gly Lys Met Trp Asn Asn Leu Lys Tyr Arg Cys Gln

	1				5				10				15				
5	AAT	CTC	TTC	AGC	CAC	GAG	GGA	GGA	AGC	CGT	AAT	GAG	AAC	GTG	GAG	ATG	212
	Asn	Leu	Phe	Ser 20	His	Glu	Gly	Gly	Ser 25	Arg	Asn	Glu	Asn	Val 30	Glu	Met	
10	AAC	CCC	AAC	AGA	TGT	CCG	TCT	GTC	AAA	GAG	AAA	AGC	ATC	AGT	CTG	GGA	260
	Asn	Pro	Asn	Arg 35	Cys	Pro	Ser	Val 40	Lys	Glu	Lys	Ser	Ile 45	Ser	Leu	Gly	
15	GAG	GCA	GCT	CCC	CAG	CAA	GAG	AGC	AGT	CCC	TTA	AGA	GAA	AAT	GTT	GCC	308
	Glu	Ala 50	Ala	Pro	Gln	Gln	Glu 55	Ser	Ser	Pro	Leu	Arg 60	Glu	Asn	Val	Ala	
20	TTA	CAG	CTG	GGA	CTG	AGC	CCT	TCC	AAG	ACC	TTT	TCC	AGG	CGG	AAC	CAA	356
	Leu	Gln	Leu	Gly	Leu	Ser 70	Pro	Ser	Lys	Thr	Phe 75	Ser	Arg	Arg	Asn	Gln 80	
25	AAC	TGT	GCC	GCA	GAG	ATC	CCT	CAA	GTG	GTT	GAA	ATC	AGC	ATC	GAG	AAA	404
	Asn	Cys	Ala	Ala	Glu 85	Ile	Pro	Gln	Val	Val 90	Glu	Ile	Ser	Ile	Glu 95	Lys	
30	GAC	AGT	GAC	TCG	GCT	GCC	ACC	CCA	GGA	ACG	AGG	CTT	GCA	CGG	AGA	GAC	452
	Asp	Ser	Asp	Ser 100	Gly	Ala	Thr	Pro	Gly 105	Thr	Arg	Leu	Ala	Arg 110	Arg	Asp	
35	TCC	TAC	TCG	CGG	CAC	GCC	CCG	TGG	GGA	GGA	AAG	AAG	AAA	CAT	TCC	TGT	500
	Ser	Tyr	Ser	Arg 115	His	Ala	Pro	Trp 120	Gly	Gly	Lys	Lys	Lys 125	His	Ser	Cys	
40	TCC	ACA	AAG	ACC	CAG	AGT	TCA	TTG	GAT	ACC	GAG	AAA	AAG	TTT	GGT	AGA	548
	Ser	Thr 130	Lys	Thr	Gln	Ser 135	Ser	Leu	Asp	Thr	Glu	Lys 140	Lys	Phe	Gly	Arg	
45	ACT	CGA	AGC	GGC	CTT	CAG	AGG	CGA	GAG	CGG	CGC	TAT	GGA	GTC	AGC	TCC	596
	Thr	Arg	Ser	Gly	Leu 150	Gln	Arg	Arg	Glu	Arg 155	Arg	Tyr	Gly	Val	Ser	Ser 160	
50	ATG	CAG	GAC	ATG	GAC	AGC	GTT	TCT	AGC	CGC	GCG	GTC	GGG	AGC	CGC	TCC	644
	Met	Gln	Asp	Met	Asp 165	Ser	Val	Ser	Ser	Arg 170	Ala	Val	Gly	Ser	Arg 175	Ser	
55	CTG	AGG	CAG	AGG	CTC	CAG	GAC	ACG	GTG	GST	TTG	TGT	TTT	CCC	ATG	AGA	692
	Leu	Arg	Gln	Arg 180	Leu	Gln	Asp	Thr	Val 185	Gly	Leu	Cys	Phe	Pro 190	Met	Arg	
60	ACT	TAC	AGC	AAG	CAG	TCA	AAG	CCA	CTC	TTT	TCC	AAT	AAA	AGA	AAA	ATC	740
	Thr	Tyr	Ser 195	Lys	Gln	Ser	Lys	Pro 200	Leu	Phe	Ser	Asn	Lys 205	Arg	Lys	Ile	
65	CAT	CTC	TCT	GAA	TTA	ATG	CTG	GAG	AAA	TGC	CCT	TTT	CCT	GCT	GGC	TCG	788
	His	Leu 210	Ser	Glu	Leu	Met 215	Glu	Lys	Lys	Cys	Pro	Phe 220	Pro	Ala	Gly	Ser	
70	GAT	TTA	GCC	CAA	AAG	TGG	CAT	TTG	ATT	AAA	CAG	CAT	ACA	GCT	CCT	GTG	836
	Asp	Leu	Ala	Gln	Lys 220	Trp 230	His	Leu	Ile	Lys 235	Gln	His	Thr	Ala	Pro 240	Val	
75	AGC	CCA	CAT	TCA	ACA	TTT	TTT	GAT	ACG	TTT	GAT	CCA	TCT	TTG	GTT	TCT	884
	Ser	Pro	His	Ser 245	Thr	Phe	Phe	Asp	Thr	Phe 250	Asp	Pro	Ser	Leu 255	Val	Ser	
80	ACA	GAA	GAT	GAA	GAA	GAT	AGG	CTT	AGA	GAG	AGA	AGG	CGG	CTT	AGT	ATT	932
	Thr	Glu	Asp	Glu	Glu	Asp	Arg	Leu	Arg	Glu	Arg	Arg	Arg	Leu	Ser	Ile	

	260	265	270	
5	GAA GAA GGG GTT GAT CCC CCT CCC AAT GCA CAA ATA CAT ACA TTT GAA Glu Glu Gly Val Asp Pro Pro Asn Ala Gln Ile His Thr Phe Glu 275 280			980
10	GCT ACT GCA CAG GTT AAT CCA TTA TTT AAA CTG GGA CCA AAA TTA GCT Ala Thr Ala Gln Val Asn Pro Leu Phe Lys Leu Gly Pro Lys Leu Ala 290 295 300			1028
15	CCT GGA ATG ACT GAA ATA AGT GGG GAC AGT TCT GCA ATT CCA CAA GCT Pro Gly Met Thr Glu Ile Ser Ser Gly Asp Ser Ser Ala Ile Pro Gln Ala 305 310 315 320			1076
20	AAT TGT GAC TCG GAA GAG GAT ACA ACC ACC CTG TGT TTG CAG TCA CGG Asn Cys Asp Ser Glu Asp Thr Thr Thr Cys Leu Gln Ser Arg 325 330 335			1124
25	AGG CAG AAG CAG CGT CAG ATA TCT GGA GAC AGC CAT ACC CAT GTT AGC Arg Gln Lys Gln Arg Gln Ile Ser Gly Asp Ser His Thr His Val Ser 340 345 350			1172
30	AGA CAG GGA GCT TGG AAA GTC CAC ACA CAG ATT GAT TAC ATA CAC TGC Arg Gln Gly Ala Trp Lys Val His Thr Gln Ile Asp Tyr Ile His Cys 355 360 365			1220
35	CTC GTG CCT GAT TTG CTT CAA ATT ACA GGG AAT CCC TGT TAC TGG GGA Leu Val Pro Asp Leu Leu Gln Ile Thr Gly Asn Pro Cys Tyr Trp Gly 370 375 380			1268
40	GTG ATG GAC CGT TAT GAA GCA GAA GCC CTC TCC GAA GGG AAA CCG GAA Val Met Asp Arg Tyr Glu Ala Glu Ala Leu Ser Ser Glu Gly Lys Pro Glu 385 390 395 400			1316
45	GGC ACG TTC TTG CTC AGG GAC TCT GCA CAG GAG GAC TAC CTC TTC TCT Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr Leu Phe Ser 405 410 415			1364
50	GTG AGT TCC GCC GCT ACA ACA GGA TCT CTG CAC GCC CGS ATC GAG CAG Val Ser Ser Ala Ala Thr Thr Gly Ser Leu His Ala Arg Ile Glu Gln 420 425 430			1412
55	TGG AAC CAC AAC TTC AGC TTC GAT GCC CAT GAC CCC TGC GTG TTT CAC Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys Val Phe His 435 440 445			1460
60	TCC TCC ACT GTC ACG GGG CTT CTC GAA CAC TAT AAA GAC CCC AGT TCG Ser Ser Thr Val Thr Gly Leu Leu Glu His Tyr Lys Asp Pro Ser Ser 450 455 460			1508
65	TGC ATG TTT TTT GAA CCG TTG CTA ACG ATA TCA CTC AAT AGG ACT TTC Cys Met Phe Phe Glu Pro Leu Leu Thr Ile Ser Leu Asn Arg Thr Phe 465 470 475 480			1556
70	CCT TTC AGC CTG CAG TAT ATC TGC CGC GCA GTG ATC TGC AGA TGC ACT Pro Phe Ser Leu Gln Tyr Ile Cys Arg Ala Val Ile Cys Arg Cys Thr 485 490 495			1604
75	ACG TAT GAT GGG ATT GAC GGG CTC CCG CTA CCG TCG ATG TTA CAG GAT Thr Tyr Asp Gly Ile Asp Gly Leu Pro Leu Pro Ser Met Leu Gln Asp 500 505 510			1652
80	TTT TTA AAA GAG TAT CAT TAT AAA CAA AAA GTT AGA GTT CGC TGG TTG Phe Leu Lys Glu Tyr His Tyr Lys Gln Lys Val Arg Val Arg Trp Leu 515 520 525 530			1700

	515	520	525	
	GAA CGA GAA CCA GTC AAG GCA AAG TAAACTCTCC GGTCCCCAAA GGGTGTTAAC			1754
5	Glu Arg Glu Pro Val Lys Ala Lys 530	535		
	TAGGTCGCT TTCATGTGCA TCAGACAGTA CACCTATAGC AAGCACACGT AGCAGTGITA			1814
	GGCTTTTTC TACAGTATGT AAGCTTAGTG TTAGTATCTG TCAGATGCTA CCTGCTGITA			1874
10	CTTATTTCAGA TAAACATGGT GCCTATTGGA ACAATAGCGG ATAGAGCTAC AGGTGTTTCAG			1934
	TAAGACTACA AAAACATTTT GCCTATTTCG CTAACAGTTT GGTTTTAAAT GGCTGTGGTA			1994
15	TTTGAGTGAG GCAACCTTGG GGCATTGTGT ATGAAGAATT CTATTCTTA CTGAAGAACA			2054
	AATAATTAAT ATTGGATGAG TATTTCACAA GTGTGACTAA TGTTTGAAAT TATTTTTC			2114
	TAAGAGTTTT TCCTATAACC TTCCAAAAGT CGTGATGTTT GTAGTTACCA TAATCCAGCT			2174
20	TTGAAGTCCA AAAGGATTAA AGGCCGCCTC CCTTGAAAA ATGCCATTTC CGGCCCAAG			2234
	GCCTAGTGCC GTCCCTCCGG			2254
25	(2) INFORMATION FOR SEQ ID NO:12:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 536 amino acids			
30	(B) TYPE: amino acid			
	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: protein			
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:			
	Met Asp Lys Val Gly Lys Met Trp Asn Asn Leu Lys Tyr Arg Cys Gln			
	1 5 10 15			
40	Asn Leu Phe Ser His Glu Gly Gly Ser Arg Asn Glu Asn Val Glu Met			
	20 25 30			
	Asn Pro Asn Arg Cys Pro Ser Val Lys Glu Lys Ser Ile Ser Leu Gly			
45	35 40 45			
	Glu Ala Ala Pro Gln Gln Glu Ser Ser Pro Leu Arg Glu Asn Val Ala			
	50 55 60			
50	Leu Gln Leu Gly Leu Ser Pro Ser Lys Thr Phe Ser Arg Arg Asn Gln			
	65 70 75 80			
	Asn Cys Ala Ala Glu Ile Pro Gln Val Glu Val Glu Ile Ser Ile Glu Lys			
	85 90 95			
55	Asp Ser Asp Ser Gly Ala Thr Pro Gly Thr Arg Leu Ala Arg Arg Asp			
	100 105 110			
	Ser Tyr Ser Arg His Ala Pro Trp Gly Gly Lys Lys His Ser Cys			
	115 120 125			
60	Ser Thr Lys Thr Gln Ser Ser Leu Asp Thr Glu Lys Lys Phe Gly Arg			
	130 135 140			
	Thr Arg Ser Gly Leu Gln Arg Arg Glu Arg Arg Tyr Gly Val Ser Ser			

	145					150					155					160
	Met	Gln	Asp	Met	Asp	Ser	Val	Ser	Ser	Arg	Ala	Val	Gly	Ser	Arg	Ser
					165					170					175	
5	Leu	Arg	Gln	Arg	Leu	Gln	Asp	Thr	Val	Gly	Leu	Cys	Phe	Pro	Met	Arg
				180					185					190		
10	Thr	Tyr	Ser	Lys	Gln	Ser	Lys	Pro	Leu	Phe	Ser	Asn	Lys	Arg	Lys	Ile
			195					200					205			
	His	Leu	Ser	Glu	Leu	Met	Leu	Glu	Lys	Cys	Pro	Phe	Pro	Ala	Gly	Ser
		210					215					220				
15	Asp	Leu	Ala	Gln	Lys	Trp	His	Leu	Ile	Lys	Gln	His	Thr	Ala	Pro	Val
		225				230					235					240
	Ser	Pro	His	Ser	Thr	Phe	Phe	Asp	Thr	Phe	Asp	Pro	Ser	Leu	Val	Ser
					245					250					255	
20	Thr	Glu	Asp	Glu	Glu	Asp	Arg	Leu	Arg	Glu	Arg	Arg	Arg	Leu	Ser	Ile
				260					265					270		
	Glu	Glu	Gly	Val	Asp	Pro	Pro	Pro	Asn	Ala	Gln	Ile	His	Thr	Phe	Glu
			275					280					285			
	Ala	Thr	Ala	Gln	Val	Asn	Pro	Leu	Phe	Lys	Leu	Gly	Pro	Lys	Leu	Ala
		290				295						300				
30	Pro	Gly	Met	Thr	Glu	Ile	Ser	Gly	Asp	Ser	Ser	Ala	Ile	Pro	Gln	Ala
		305				310					315					320
	Asn	Cys	Asp	Ser	Glu	Glu	Asp	Thr	Thr	Thr	Leu	Cys	Leu	Gln	Ser	Arg
					325					330					335	
35	Arg	Gln	Lys	Gln	Arg	Gln	Ile	Ser	Gly	Asp	Ser	His	Thr	His	Val	Ser
				340					345					350		
40	Arg	Gln	Gly	Ala	Trp	Lys	Val	His	Thr	Gln	Ile	Asp	Tyr	Ile	His	Cys
			355					360					365			
	Leu	Val	Pro	Asp	Leu	Leu	Gln	Ile	Thr	Gly	Asn	Pro	Cys	Tyr	Trp	Gly
		370					375					380				
45	Val	Met	Asp	Arg	Tyr	Glu	Ala	Glu	Ala	Leu	Ser	Glu	Gly	Lys	Pro	Glu
		385				390					395					400
	Gly	Thr	Phe	Leu	Leu	Arg	Asp	Ser	Ala	Gln	Glu	Asp	Tyr	Leu	Phe	Ser
				405						410					415	
50	Val	Ser	Ser	Ala	Ala	Thr	Thr	Gly	Ser	Leu	His	Ala	Arg	Ile	Glu	Gln
				420					425					430		
	Trp	Asn	His	Asn	Phe	Ser	Phe	Asp	Ala	His	Asp	Pro	Cys	Val	Phe	His
			435					440					445			
	Ser	Ser	Thr	Val	Thr	Gly	Leu	Leu	Glu	His	Tyr	Lys	Asp	Pro	Ser	Ser
		450				455						460				
60	Cys	Met	Phe	Phe	Glu	Pro	Leu	Leu	Thr	Ile	Ser	Leu	Asn	Arg	Thr	Phe
		465				470					475					480
	Pro	Phe	Ser	Leu	Gln	Tyr	Ile	Cys	Arg	Ala	Val	Ile	Cys	Arg	Cys	Thr
				485						490					495	

Thr Tyr Asp Gly Ile Asp Gly Leu Pro Leu Pro Ser Met Leu Gln Asp
500 505 510

5 Phe Leu Lys Glu Tyr His Tyr Lys Gln Lys Val Arg Val Arg Trp Leu
515 520 525

Glu Arg Glu Pro Val Lys Ala Lys
530 535

10 (2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 2206 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
25 (A) NAME/KEY: CDS
(B) LOCATION: 2..1375

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2078
30 (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
or G at positions: 2078, and 2116."

(ix) FEATURE:
(A) NAME/KEY: misc_feature
35 (B) LOCATION: 2063
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at
position 2063."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

40 G GAG CGC GGC CTG GAG ACT AAC AGC TGC TCG GAA GAG GAG CTC AGC 46
Glu Arg Gly Leu Glu Thr Asn Ser Cys Ser Glu Glu Glu Leu Ser
1 5 10 15

45 AGC CCG GGT CGC GGA GGA GGA GGG GGC GGC CGG CTT CTG CTG CAG CCC 94
Ser Pro Gly Arg Gly Gly Gly Gly Gly Arg Leu Leu Leu Gln Pro
20 25 30

50 CCA GGC CCT GAA TTA CCT CGG GTG CCC TTC CGG CTG CAG GAC TTG GTC 142
Pro Gly Pro Glu Leu Pro Pro Val Pro Phe Pro Leu Gln Asp Leu Val
35 40 45

55 CCT CTG GGG CGC CTG AGT AGA GGG GAG CAG CAG CAG CAG CAG CAG 190
Pro Leu Gly Arg Leu Ser Arg Gly Glu Gln Gln Gln Gln Gln Gln
50 55 60

CAA CCT CCC CGC CCC CGG CCT CCT CCC GGG CCC CTC CGG CCA GTC GCG 238
Gln Pro Pro Pro Pro Pro Pro Pro Gly Pro Leu Arg Pro Leu Ala
65 70 75

60 GGT CCT TCT CGG AAG GGC TCC TTC AAA ATC CGC CTC AGT CGC CTC TTT 286
Gly Pro Ser Arg Lys Gly Ser Phe Lys Ile Arg Leu Ser Arg Leu Phe
80 85 90 95

	CGC ACC AAG AGC TGC AAC GGT GGC TCC GGC GGT GGG GAT GGG ACC GGC	334
	Arg Thr Lys Ser Cys Asn Gly Gly Ser Gly Gly Asp Gly Thr Gly	
	100	110
5	AAG AGG CCT TCT GGA GAG CTG GCT GCT TCA GCT GCG AGC CTG ACA GAC	382
	Lys Arg Pro Ser Gly Glu Leu Ala Ser Ala Ala Ser Leu Thr Asp	
	115	125
10	ATG GGA GGC TCT GCG GGC CGG GAG CTG GAC GCG GGG AGG AAA CCC AAG	430
	Met Gly Gly Ser Ala Gly Arg Glu Leu Asp Ala Gly Arg Lys Pro Lys	
	130	135
	145	155
15	TTG ACA AGA ACT CAA AGT GCC TTT TCT CCG GTC TCC TTC AGC CCC CTG	478
	Leu Thr Arg Thr Gln Ser Ala Phe Ser Pro Val Ser Phe Ser Pro Leu	
	145	155
	165	175
20	TTC ACA GGT GAA ACT GTG TCG CTT GTG GAT GTG GAC ATT TCT CAG CGG	526
	Phe Thr Gly Glu Thr Val Ser Leu Val Asp Val Asp Ile Ser Gln Arg	
	160	175
	180	190
	185	190
25	AGC CTC AGC CTC CTA GAT GAT ATC AGT GGG ACG CTG CCT ACA TCT GTC	622
	Ser Leu Ser Leu Leu Asp Asp Ile Ser Gly Thr Leu Pro Thr Ser Val	
	195	205
	210	220
30	CTT GTG GCT CCG ATG GGG TCT TCC TTG CAG TCT TTC CCC CTA CCT CCG	670
	Leu Val Ala Pro Met Gly Ser Ser Leu Gln Ser Phe Pro Leu Pro Pro	
	210	215
	225	235
35	CCT CCT CCA CCC CAT GCC CCA GAT GCA TTT CCC CGG ATT GCT CCC ATC	718
	Pro Pro Pro Pro His Ala Pro Asp Ala Phe Pro Arg Ile Ala Pro Ile	
	225	235
	240	250
	255	265
40	CGA GCA GCT GAA TCC CTG CAC AGC CAA CCC CCA CAG CAC CTC CAG TGT	766
	Arg Ala Ala Glu Ser Leu His Ser Gln Pro Pro Gln His Leu Gln Cys	
	240	255
	260	270
	275	285
45	TTG GAG AAG TGT GGT TGG TAT TGG GGG CCA ATG AAT TGG GAA GAT GCA	862
	Leu Glu Lys Cys Gly Trp Tyr Trp Gly Pro Met Asn Trp Glu Asp Ala	
	275	285
	290	300
50	GAG ATG AAG CTG AAA GGG AAA CCA GAT GGT TCT TTC CTG GTA CGA GAC	910
	Glu Met Lys Lys Leu Lys Gly Lys Pro Asp Gly Ser Phe Leu Val Arg Asp	
	290	300
	310	315
55	AGT TCT GAT CCT CGT TAC ATC CTG AGC CTC AGT TTC CGA TCA CAG GGT	958
	Ser Ser Asp Pro Arg Tyr Ile Leu Ser Leu Ser Phe Arg Ser Gln Gly	
	305	315
	320	335
	340	350
60	ATC ACC CAC CAC ACT AGA ATG GAG CAC TAC AGA GGA ACC TTC AGC CTG	1006
	Ile Thr His His Thr Arg Met Glu His Tyr Arg Gly Thr Phe Ser Leu	
	320	335
	345	350
	355	360
	365	370
	375	380
	385	390
	395	400
	405	410
	415	420
	425	430
	435	440
	445	450
	455	460
	465	470
	475	480
	485	490
	495	500
	505	510
	515	520
	525	530
	535	540
	545	550
	555	560
	565	570
	575	580
	585	590
	595	600
	605	610
	615	620
	625	630
	635	640
	645	650
	655	660
	665	670
	675	680
	685	690
	695	700
	705	710
	715	720
	725	730
	735	740
	745	750
	755	760
	765	770
	775	780
	785	790
	795	800
	805	810
	815	820
	825	830
	835	840
	845	850
	855	860
	865	870
	875	880
	885	890
	895	900
	905	910
	915	920
	925	930
	935	940
	945	950
	955	960
	965	970
	975	980
	985	990
	995	1000

	ATT AAG AGA GCC ATT ATG CAC TCC AAG AAT GGA AAG TTT CTC TAT TTC Ile Lys Arg Ala Ile Met His Ser Lys Asn Gly Lys Phe Leu Tyr Phe 355 360 365	1102
5	TTA AGA TCC AGG GTT CCA GGA CTG CCA CCA ACT CCT GTC CAG CTG CTC Leu Arg Ser Arg Val Pro Gly Leu Pro Pro Thr Pro Val Gln Leu Leu 370 375 380	1150
10	TAT CCA GTG TCC CGA TTC AGC AAT GTC AAA TCC CTC CAG CAC CTT TGC Tyr Pro Val Ser Arg Phe Ser Asn Val Lys Ser Leu Gln His Leu Cys 385 390 395	1198
15	AGA TTC CGG ATA CGA CAG CTC GTC AGG ATA GAT CAC ATC CCA GAT CTC Arg Phe Arg Ile Arg Gln Leu Val Arg Ile Asp His Ile Pro Asp Leu 400 405 410 415	1246
20	CCA CTG CCT AAA CCT CTG ATC TCT TAT ATC CGA AAG TTC TAC TAC TAT Pro Leu Pro Lys Pro Leu Ile Ser Tyr Ile Arg Lys Phe Tyr Tyr Tyr 420 425 430	1294
	GAT CCT CAG GAA GAG GTA TAC CTG TCT CTA AAG GAA GCG CAG CTC ATT Asp Pro Gln Glu Glu Val Tyr Leu Ser Leu Lys Glu Ala Gln Leu Ile 435 440 445	1342
25	TCC AAA CAG AAG CAA GAG GTG GAA CCC TCC ACG TAGCGAGGGG CTCCTGCTG Ser Lys Gln Lys Gln Glu Val Glu Pro Ser Thr 450 455	1395
30	GTCACCACCA AGGGCATTGT GTTGCCAAGC TCCAGCTTTG AAGAACCATA TTAAGCTACC ATGAAAAGAA GAGGAAAGT GAGGGAACAG GAAGGTTGGG ATTCTCTGTG CAGAGACTTT GGTTCCCCAC GCAGCCCTGG GCCTTGAAG AAGCACATGA CCGTACTCTG CGTGGGGCTC	1455 1515 1575
35	CACCTCACAC CCACCCCTGG GCATCTTAGG ACTGGAGGGG CTCCTTGGAA AACTGGAAGA AGTCTCAACA CTGTTTCTTT TTTAAAAAAA AAAAAAAAAA AGATGCGGCC GCAAGCTTAT	1635 1695
40	TCCCTTTAGT GAGGGTAAAT TTTAGCTTGG CACTGGCCGT CGTTTACAAA CGTCGTGACT GGGAAAACCC TGCGGTTACC CAACCTAATC GCCTTGCAGC ACATCCCCCT TTCGCCAGCT GGCGTAATAG CGAAGAGGCC CGCACCAGTC GCCCTTCCCA ACAGTTGCGC AGCCTGAATG	1755 1815 1875
45	GCGAATGGGA CGCGCCCTGT AGCGGCGCAT TAACGCGCGG CGGGGTGTGGT GGTACGCGC AGCGTGACCG CTACACTTGC CAGCGCCCTA CGCCCGCTCC TTTCGCTTTC TTCCCTTCCT	1935 1995
50	TTCTCGCCAC GTTTCGCGGC TTTCCCGTTC AACTCTAAAT CGGGGGCTCC CTTTAGGTTT CGATTTACTG CTTTACGCAC TCCACCCCAA AACTTGATTA GGTGATGTCA CTTATGGCAC CCCTGATAAC GTTTCCTTCT ACTTTGATCA CTTCTTTATA TGATCTTTCC AATGAAACAT	2055 2115 2175
55	CACCTACTCG TCATCTTTAT TTAAGATTT G	2206

(2) INFORMATION FOR SEQ ID NO:14:

- 60 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 458 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

5	Glu 1	Arg	Gly	Leu	Glu 5	Thr	Asn	Ser	Cys	Ser 10	Glu	Glu	Glu	Leu	Ser 15	Ser
10	Pro	Gly	Arg	Gly 20	Gly	Gly	Gly	Gly	Gly 25	Arg	Leu	Leu	Leu	Gln 30	Pro	Pro
	Gly	Pro	Glu 35	Leu	Pro	Pro	Val	Pro	Phe 40	Pro	Leu	Gln	Asp 45	Leu	Val	Pro
15	Leu	Gly 50	Arg	Leu	Ser	Arg	Gly 55	Glu	Gln	Gln	Gln	Gln 60	Gln	Gln	Gln	Gln
	Pro 65	Pro	Pro	Pro	Pro	Pro 70	Pro	Pro	Gly	Pro	Leu 75	Arg	Pro	Leu	Ala	Gly 80
20	Pro	Ser	Arg	Lys 85	Gly	Ser	Phe	Lys	Ile	Arg 90	Leu	Ser	Arg	Leu	Phe 95	Arg
25	Thr	Lys	Ser	Cys 100	Asn	Gly	Gly	Ser	Gly 105	Gly	Gly	Asp	Gly	Thr 110	Gly	Lys
	Arg	Pro	Ser 115	Gly	Glu	Leu	Ala	Ala 120	Ser	Ala	Ala	Ser	Leu 125	Thr	Asp	Met
30	Gly	Gly 130	Ser	Ala	Gly	Arg	Glu 135	Leu	Asp	Ala	Gly	Arg 140	Lys	Pro	Lys	Leu
	Thr 145	Arg	Thr	Gln	Ser	Ala 150	Phe	Ser	Pro	Val	Ser 155	Phe	Ser	Pro	Leu	Phe 160
35	Thr	Gly	Glu	Thr 165	Val	Ser	Leu	Val	Asp 170	Val	Asp	Ile	Ser	Gln	Arg 175	Gly
	Leu	Thr	Ser 180	Pro	His	Pro	Pro	Thr	Pro 185	Pro	Pro	Pro	Pro	Arg 190	Arg	Ser
40	Leu	Ser	Leu 195	Leu	Asp	Asp	Ile	Ser 200	Gly	Thr	Leu	Pro 205	Thr	Ser	Val	Leu
	Val 210	Ala	Pro	Met	Gly	Ser	Ser 215	Leu	Gln	Ser	Phe	Pro 220	Leu	Pro	Pro	Pro
	Pro 225	Pro	Pro	His	Ala 230	Pro	Asp	Ala	Phe	Pro	Arg 235	Ile	Ala	Pro	Ile	Arg 240
50	Ala	Ala	Glu	Ser 245	Leu	His	Ser	Gln	Pro	Pro 250	Gln	His	Leu	Gln	Cys 255	Pro
	Leu	Tyr	Arg	Pro 260	Asp	Ser	Ser	Ser	Phe 265	Ala	Ala	Ser	Leu	Arg 270	Glu	Leu
55	Glu	Lys	Cys 275	Gly	Trp	Tyr	Trp	Gly 280	Pro	Met	Asn	Trp	Glu 285	Asp	Ala	Glu
	Met 290	Lys	Leu	Lys	Gly	Lys	Pro 295	Asp	Gly	Ser	Phe 300	Leu	Val	Arg	Asp	Ser
60	Ser 305	Asp	Pro	Arg	Tyr	Ile 310	Leu	Ser	Leu	Ser	Phe 315	Arg	Ser	Gln	Gly	Ile 320

Thr His His Thr Arg Met Glu His Tyr Arg Gly Thr Phe Ser Leu Trp
 325 330
 5 Cys His Pro Lys Phe Glu Asp Arg Cys Gln Ser Val Val Glu Phe Ile
 340 345 350
 Lys Arg Ala Ile Met His Ser Lys Asn Gly Lys Phe Leu Tyr Phe Leu
 355 360 365
 10 Arg Ser Arg Val Pro Gly Leu Pro Pro Thr Pro Val Gln Leu Leu Tyr
 370 375 380
 Pro Val Ser Arg Phe Ser Asn Val Lys Ser Leu Gln His Leu Cys Arg
 385 390 395 400
 15 Phe Arg Ile Arg Gln Leu Val Arg Ile Asp His Ile Pro Asp Leu Pro
 405 410 415
 Leu Pro Lys Pro Leu Ile Ser Tyr Ile Arg Lys Phe Tyr Tyr Tyr Asp
 420 425 430
 20 Pro Gln Glu Glu Val Tyr Leu Ser Leu Lys Glu Ala Gln Leu Ile Ser
 435 440 445
 25 Lys Gln Lys Gln Glu Val Glu Pro Ser Thr
 450 455

(2) INFORMATION FOR SEQ ID NO:15:

30 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1390 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- 40 (A) NAME/KEY: CDS
 (B) LOCATION: 453..1388

(ix) FEATURE:

- 45 (A) NAME/KEY: misc_feature
 (B) LOCATION: 108
 (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
 or G at positions: 108, and 109."

(ix) FEATURE:

- 50 (A) NAME/KEY: misc_feature
 (B) LOCATION: 236
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or G at
 positions: 236, 238, and 1258."

55

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
 (B) LOCATION: 233
 (D) OTHER INFORMATION: /note= "Nucleotide may be G or T at
 position 233."

60

(ix) FEATURE:

- (A) NAME/KEY: misc_feature
 (B) LOCATION: 234
 (D) OTHER INFORMATION: /note= "Nucleotide may be G or C at

position 234."

(ix) FEATURE:

- 5 (A) NAME/KEY: misc_feature
(B) LOCATION: 237
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at position 237."

(ix) FEATURE:

- 10 (A) NAME/KEY: misc_feature
(B) LOCATION: 239
(D) OTHER INFORMATION: /note= "Nucleotide may be A or T at position 239."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

	CGGACGCGTG GGTGTCGCTG TGAATATCTCT ATTTGCTTGC AGTATCTGTT TCTCTTCCTA	60
20	GGCTCAAGTT GGTGACCCAA GCCTATTGTA AACAAAGTAT TATCTCACCG GGAGATGCCA	120
	ATGGAGTAAC AATTGTGTTAA CCTTACGTTT TCTGTCTGTA TATTTTAAAA AAAATCTGGT	180
25	AGTTTCTGGA AAAAAAGAG AAGGGGGTTT GTAGTACTTA ACCCTATTTT TGGCCACGAG	240
	TTTTAGTTAA TTAGTTTTTG GAATAAATGG ATTTTCAGTAT AGCTTTGTGG TTAATTTGCA	300
	TTGCCTTTAT TTTATGTTTA GGCTTATTTT TAAATTAACA TTTAACAGAA ACATTTGAAA	360
30	TAGAATTTGC ATGCTCGCCT TAATTAACCT AAAGACTGAT TTTAATCTGA CTATGACACT	420
	GAGCATATTC TTTAAATTAC TCATAATTTA TA ATG CTT AAT ATA ATC TTA ATT	473
	Met Leu Asn Ile Ile Leu Ile	
	1 5	
35	AAA TTT AGC AGT TTT AGT ATA AGA TGT GCC ATT TTG TCC TCT GTA TGT	521
	Lys Phe Ser Ser Phe Ser Ile Arg Cys Ala Ile Leu Ser Ser Val Cys	
	10 15 20	
40	CTG AAT GAA GCT ATA ACA TTT GCC TTT TTA TTG CAG GTT TTC CTT TGG	569
	Leu Asn Glu Ala Ile Thr Phe Ala Phe Leu Leu Gln Val Phe Leu Trp	
	25 30 35	
45	AAT ATG GAT AAA TAC ACC ATG ATA CGS AAA CTA GAA GGA CAT CAC CAT	617
	Asn Met Asp Lys Tyr Thr Met Ile Arg Lys Leu Glu Gly His His His	
	40 45 50 55	
	GAT GTG GTA GCT TGT GAC TTT TCT CCT GAT GGA GCA TTA CTG GCT ACT	665
50	Asp Val Val Ala Cys Asp Phe Ser Pro Asp Gly Ala Leu Leu Ala Thr	
	60 65 70	
	GCA TCT TAT GAT ACT CGA GTA TAT ATC TGG GAT CCA CAT AAT GGA GAC	713
	Ala Ser Tyr Asp Thr Arg Val Tyr Ile Trp Asp Pro His Asn Gly Asp	
	75 80 85	
55	ATT CTG ATG GAA TTT GGG CAC CTG TTT CCC CCA CCT ACT CCA ATA TTT	761
	Ile Leu Met Glu Phe Gly His Leu Phe Pro Pro Thr Pro Ile Phe	
	90 95 100	
60	GCT GGA GGA GCA AAT GAC CGG TGG GTA CGA TCT GTA TCT TTT AGC CAT	809
	Ala Gly Gly Ala Asn Asp Arg Trp Val Arg Ser Val Ser Phe Ser His	
	105 110 115	
	GAT GGA CTG CAT GTT GCA AGC CTT GCT GAT GAT AAA ATG GTG AGG TTC	857

	Asp Gly Leu His Val Ala Ser Leu Ala Asp Asp Lys Met Val Arg Phe 120 125 130 135	
5	TGG AGA ATT GAT GAG GAT TAT CCA GTG CAA GTT GCA CCT TTG AGC AAT Trp Arg Ile Asp Glu Asp Tyr Pro Val Gln Val Ala Pro Leu Ser Asn 140 145 150	905
10	GGT CTT TGC TGT GCC TTC TCT ACT GAT GGC AGT GTT TTA GCT GCT GGG Gly Leu Cys Cys Ala Phe Ser Thr Asp Gly Ser Val Leu Ala Ala Gly 155 160 165	953
15	ACA CAT GAC GGA AGT GTG TAT TTT TGG GCC ACT CCA CGG CAG GTC CCT Thr His Asp Gly Ser Val Tyr Phe Trp Ala Thr Pro Arg Gln Val Pro 170 175 180	1001
20	AGC CTG CAA CAT TTA TGT CGC ATG TCA ATC CGA AGA GTG ATG CCC ACC Ser Leu Gln His Leu Cys Arg Met Ser Ile Arg Arg Val Met Pro Thr 185 190 195	1049
25	CAA GAA GTT CAG GAG CTG CCG ATT CCT TCC AAG CTT TTG GAG TTT CTC Gln Glu Val Gln Glu Leu Pro Ile Pro Ser Lys Leu Leu Glu Phe Leu 200 205 210 215	1097
30	TCG TAT CGT ATT TAG AAG ATT CTG CCT TCC CTA GTA GTA GGG ACT GAC Ser Tyr Arg Ile * Lys Ile Leu Pro Ser Leu Val Val Gly Thr Asp 220 225 230	1145
35	AGA ATA CAC TTA ACA CAA ACC TCA AGC TTT ACT GAC TTC AAT TAT CTG Arg Ile His Leu Thr Gln Thr Ser Ser Phe Thr Asp Phe Asn Tyr Leu 235 240 245	1193
40	TTT TTA AAG ACG TAG AAG ATT TAT TTA ATT TGA TAT GTT CTT GTA CTG Phe Leu Lys Thr * Lys Ile Tyr Leu Ile * Tyr Val Leu Val Leu 250 255 260	1241
45	CAT TTT GAT CAG TTG AAG CTT TTA AAA TAT TAT TTA TAG ACA ATA GAA His Phe Asp Gln Leu Lys Leu Leu Lys Tyr Tyr Leu * Thr Ile Glu 265 270 275	1289
50	GTA TTT CTG AAC ATA TCA AAT ATA AAT TTT TTT AAA GAT CTA ACT GTG Val Phe Leu Asn Ile Ser Asn Ile Asn Phe Phe Lys Asp Leu Thr Val 280 285 290 295	1337
55	AAA AAC ATA CAT ACC TGT ACA TAT TTA GAT ATA AGC TGC TAT ATG TTG Lys Asn Ile His Thr Cys Thr Tyr Leu Asp Ile Ser Cys Tyr Met Leu 300 305 310	1385
60	AAT GG Asn	1390

(2) INFORMATION FOR SEQ ID NO:16:

- 55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 312 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

- 60 (ii) MOLECULE TYPE: protein

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Leu Asn Ile Ile Leu Ile Lys Phe Ser Ser Phe Ser Ile Arg Cys

	1	5	10	15
	Ala Ile Leu Ser	Ser Val Cys	Leu Asn Glu Ala	Ile Thr Phe Ala Phe
	20		25	30
5	Leu Leu Gln Val	Phe Leu Trp	Asn Met Asp Lys	Tyr Thr Met Ile Arg
	35		40	45
10	Lys Leu Glu Gly	His His His	Asp Val Val Ala	Cys Asp Phe Ser Pro
	50		55	60
	Asp Gly Ala Leu	Leu Ala Thr	Ala Ser Tyr Asp	Thr Arg Val Tyr Ile
	65	70	75	80
15	Trp Asp Pro His	Asn Gly Asp	Ile Leu Met Glu	Phe Gly His Leu Phe
		85	90	95
	Pro Pro Pro Thr	Pro Ile Phe	Ala Gly Gly Ala	Asn Asp Arg Trp Val
	100		105	110
20	Arg Ser Val Ser	Phe Ser His	Asp Gly Leu His	Val Ala Ser Leu Ala
	115		120	125
	Asp Asp Lys Met	Val Arg Phe	Trp Arg Ile Asp	Glu Asp Tyr Pro Val
	130		135	140
	Gln Val Ala Pro	Leu Ser Asn	Gly Leu Cys Cys	Ala Phe Ser Thr Asp
	145	150	155	160
30	Gly Ser Val Leu	Ala Ala Gly	Thr His Asp Gly	Ser Val Tyr Phe Trp
		165	170	175
	Ala Thr Pro Arg	Gln Val Pro	Ser Leu Gln His	Leu Cys Arg Met Ser
	180		185	190
35	Ile Arg Arg Val	Met Pro Thr	Gln Glu Val Gln	Glu Leu Pro Ile Pro
	195		200	205
	Ser Lys Leu Leu	Glu Phe Leu	Ser Tyr Arg Ile	* Lys Ile Leu Pro
	210		215	220
	Ser Leu Val Val	Gly Thr Asp	Arg Ile His Leu	Thr Gln Thr Ser Ser
	225	230	235	240
45	Phe Thr Asp Phe	Asn Tyr Leu	Phe Leu Lys Thr	* Lys Ile Tyr Leu
		245	250	255
	Ile * Tyr Val	Leu Val Leu	His Phe Asp Gln	Leu Lys Leu Lys
	260		265	270
50	Tyr Tyr Leu *	Thr Ile Glu	Val Phe Leu Asn	Ile Ser Asn Ile Asn
	275		280	285
	Phe Phe Lys Asp	Leu Thr Val	Lys Asn Ile His	Thr Cys Thr Tyr Leu
	290		295	300
	Asp Ile Ser Cys	Tyr Met Leu	Asn	
	305	310		
60	(2) INFORMATION FOR SEQ ID NO:17:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 257 amino acids			
	(B) TYPE: amino acid			

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

10

Met Val Leu Cys Val Gln Gly Ser Cys Pro Leu Leu Ala Val Gln
1 5 10 15

15

Ile Gly Arg Arg Pro Leu Trp Ala Gln Ser Leu Glu Leu Pro Gly Pro
20 25 30Ala Met Gln Pro Leu Pro Thr Gly Ala Phe Pro Glu Glu Val Thr Glu
35 40 45

20

Glu Thr Pro Val Gln Ala Glu Asn Glu Pro Lys Val Leu Asp Pro Glu
50 55 60Gly Asp Leu Leu Cys Ile Ala Lys Thr Phe Ser Tyr Leu Arg Glu Ser
65 70 75 80

25

Gly Trp Tyr Trp Gly Ser Ile Thr Ala Ser Glu Ala Arg Gln His Leu
85 90 95

30

Gln Lys Met Pro Glu Gly Thr Phe Leu Val Arg Asp Ser Thr His Pro
100 105 110Ser Tyr Leu Phe Thr Leu Ser Val Lys Thr Thr Arg Gly Pro Thr Asn
115 120 125

35

Val Arg Ile Glu Tyr Ala Asp Ser Ser Phe Arg Leu Asp Ser Asn Cys
130 135 140Leu Ser Arg Pro Arg Ile Leu Ala Phe Pro Asp Val Val Ser Leu Val
145 150 155 160

40

Gln His Tyr Val Ala Ser Cys Ala Ala Asp Thr Arg Ser Asp Ser Pro
165 170 175Asp Pro Ala Pro Thr Pro Ala Leu Pro Met Ser Lys Gln Asp Ala Pro
180 185 190

45

Ser Asp Ser Val Leu Pro Ile Pro Val Ala Thr Ala Val His Leu Lys
195 200 205

50

Leu Val Gln Pro Phe Val Arg Ser Ser Ala Arg Ser Leu Gln His
210 215 220Leu Cys Arg Leu Val Ile Asn Arg Leu Val Ala Asp Val Asp Cys Leu
225 230 235 240

55

Pro Leu Pro Arg Arg Met Ala Asp Tyr Leu Arg Gln Tyr Pro Phe Gln
245 250 255

60

Leu

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 211 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

15

Met Val Ala His Asn Gln Val Ala Ala Asp Asn Ala Val Ser Thr Ala
 1 5 10 15

20

Ala Glu Pro Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
 20 25 30

25

Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Ala Val Pro Ala Pro
 35 40 45

Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ala Asp Tyr
 50 55 60

30

Arg Arg Ile Thr Arg Ala Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr
 65 70 75 80

Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu
 85 90 95

35

Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe
 100 105 110

Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val
 115 120 125

His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Ser Phe
 130 135 140

40

Asp Cys Leu Phe Glu Leu Glu His Tyr Val Ala Ala Pro Arg Arg
 145 150 155 160

Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu
 165 170 175

45

Leu Cys Arg Gln Arg Ile Val Ala Thr Val Gly Arg Glu Asn Leu Ala
 180 185 190

50

Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro
 195 200 205

Phe Gln Ile
 210

55 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

60

- (A) LENGTH: 212 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

5 Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala
1 5 10

10 Ala Glu Pro Arg Arg Arg Ser Glu Pro Ser Ser Ser Ser Ser Ser Ser
20 25 30

Ser Pro Ala Ala Pro Val Arg Pro Arg Pro Cys Pro Ala Val Pro Ala
35 40 45

15 Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
50 55 60

Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
65 70 75 80

20 Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
85 90 95

25 Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
100 105 110

Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
115 120 125

30 Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
130 135 140

Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
145 150 155 160

35 Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
165 170 175

40 Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
180 185 190

Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
195 200 205

45 Pro Phe Gln Ile
210

(2) INFORMATION FOR SEQ ID NO:20:

50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 306 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

55 (ii) MOLECULE TYPE: peptide

60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Ala Leu Ser Pro Ala Ala Thr Leu Thr Ala Trp Pro Ala Asp Ser Ala
1 5 10 15

Arg Arg Gly Pro Gly Cys Thr Ala Ser Gly Tyr Pro Val Pro Ala Ala
 20 25 30
 5 Arg Ala Pro Ala Ala Gly Asp Gln Trp Val Thr Ala Ala Ala Arg Asp
 35 40 45
 Phe Val Ile Arg Pro Pro Gly Ser Gly Glu Lys Glu Pro His Pro Phe
 50 55 60
 10 Ser Leu Cys His His Phe Gly His Pro Ala Gly Leu Val Leu Gly Phe
 65 70 75 80
 15 Ala Leu Thr Ser Arg Lys Asp Ala Asn Pro Ser Leu Thr Pro Ala Arg
 85 90 95
 Ala Ala Thr Cys Leu Cys Arg Gly Asp Pro Ser Leu Met Thr Leu Arg
 100 105 110
 20 Cys Leu Glu Pro Ser Gly Asn Gly Gly Glu Gly Thr Arg Ser Gln Trp
 115 120 125
 Gly Thr Ala Gly Ser Ala Glu Glu Pro Ser Pro Gln Ala Ala Arg Leu
 130 135 140
 25 Ala Lys Ala Leu Arg Glu Leu Gly Gln Thr Gly Trp Tyr Trp Gly Ser
 145 150 155 160
 30 Met Thr Val Asn Glu Ala Lys Glu Lys Leu Lys Glu Ala Pro Glu Gly
 165 170 175
 Thr Phe Leu Ile Arg Asp Ser Ser His Ser Asp Tyr Leu Leu Thr Ile
 180 185 190
 35 Ser Val Lys Thr Ser Ala Gly Pro Thr Asn Leu Arg Ile Glu Tyr Gln
 195 200 205
 Asp Gly Lys Phe Arg Leu Asp Ser Ile Ile Cys Val Lys Ser Lys Leu
 210 215 220
 40 Lys Gln Phe Asp Ser Val Val His Leu Ile Asp Tyr Tyr Val Gln Met
 225 230 235 240
 Cys Lys Asp Lys Arg Thr Gly Pro Glu Ala Pro Arg Asn Gly Thr Val
 245 250 255
 45 His Leu Tyr Leu Thr Lys Pro Leu Tyr Thr Ser Ala Pro Ser Leu Gln
 260 265 270
 50 His Leu Cys Arg Leu Thr Ile Asn Lys Cys Thr Gly Ala Ile Trp Gly
 275 280 285
 Leu Pro Leu Pro Thr Arg Leu Lys Asp Tyr Leu Glu Glu Tyr Lys Phe
 290 295 300
 55 Gln Val
 305

(2) INFORMATION FOR SEQ ID NO:21:

60

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 225 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

10 Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu
 1 5 10 15

Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
 20 25 30

15 Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
 35 40 45

20 Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Ser Ala Glu Pro
 50 55 60

Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
 65 70 75 80

25 Ala Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
 85 90 95

Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
 100 105 110

30 Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met
 115 120 125

35 Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser
 130 135 140

Ser Glu Val Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro
 145 150 155 160

40 Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
 165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
 180 185 190

45 Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
 195 200 205

50 Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
 210 215 220

Leu
 225

55 (2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 225 amino acids

(B) TYPE: amino acid

60 (C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

5 Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu
1 5 10 15

10 Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
20 25 30

Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
35 40 45

15 Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
50 55 60

Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
65 70 75 80

20 Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
85 90 95

25 Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
100 105 110

Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val His His Tyr Met
115 120 125

30 Pro Pro Pro Gly Thr Pro Ser Phe Ser Leu Pro Pro Thr Glu Pro Ser
130 135 140

Ser Glu Val Pro Glu Gln Pro Pro Ala Gln Ala Leu Pro Gly Ser Thr
145 150 155 160

35 Pro Lys Arg Ala Tyr Tyr Ile Tyr Ser Gly Glu Lys Ile Pro Leu
165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

40 Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

45 Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

Leu
225

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- 55 (A) LENGTH: 510 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

	Leu	Tyr	Trp	Ser	Ser	Thr	Val	Val	Ala	Ala	Ala	Leu	Glu	Xaa	Xaa	Xaa	
	1				5					10						15	
5	Xaa	Xaa	Gly	Cys	Xaa	Xaa	Xaa	Glu	Xaa	Glu	Gly	Val	Arg	Ser	Ser	Pro	
				20					25					30			
	Val	Val	Ser	Leu	Ser	Leu	Pro	Leu	Xaa	Arg	Ala	Arg	Met	Gly	Arg	Ala	
			35					40					45				
10	Glu	Leu	Leu	Glu	Gly	Lys	Met	Ser	Thr	Gln	Asp	Pro	Ser	Asp	Leu	Trp	
		50					55					60					
15	Ser	Arg	Ser	Asp	Gly	Glu	Ala	Glu	Leu	Leu	Gln	Asp	Leu	Gly	Trp	Tyr	
	65					70					75					80	
	His	Gly	Asn	Leu	Thr	Arg	His	Ala	Ala	Glu	Ala	Leu	Leu	Leu	Ser	Asn	
					85					90					95		
20	Gly	Cys	Asp	Gly	Ser	Tyr	Leu	Leu	Arg	Asp	Ser	Asn	Glu	Thr	Thr	Gly	
				100					105					110			
	Leu	Tyr	Ser	Leu	Ser	Val	Arg	Ala	Lys	Asp	Ser	Val	Lys	His	Phe	His	
			115					120					125				
25	Val	Glu	Tyr	Thr	Gly	Tyr	Ser	Phe	Lys	Phe	Gly	Phe	Asn	Glu	Phe	Ser	
		130					135					140					
30	Ser	Leu	Lys	Asp	Phe	Val	Lys	His	Phe	Ala	Asn	Gln	Pro	Leu	Ile	Gly	
		145				150					155					160	
	Ser	Glu	Thr	Gly	Thr	Leu	Met	Val	Leu	Lys	His	Pro	Tyr	Pro	Arg	Lys	
				165						170					175		
35	Val	Xaa	Glu	Pro	Ser	Ile	Tyr	Glu	Ser	Val	Arg	Val	His	Thr	Ala	Met	
				180					185					190			
	Gln	Thr	Gly	Arg	Thr	Glu	Asp	Asp	Leu	Val	Pro	Thr	Ala	Pro	Ser	Leu	
			195					200					205				
40	Gly	Thr	Lys	Glu	Gly	Tyr	Leu	Thr	Lys	Gln	Gly	Gly	Leu	Val	Lys	Thr	
		210					215					220					
45	Trp	Lys	Thr	Arg	Trp	Phe	Thr	Leu	His	Arg	Asn	Glu	Leu	Lys	Tyr	Phe	
	225					230					235					240	
	Lys	Asp	Gln	Met	Ser	Pro	Glu	Pro	Ile	Arg	Ile	Leu	Asp	Leu	Thr	Glu	
				245						250				255			
50	Cys	Ser	Ala	Val	Gln	Phe	Asp	Tyr	Ser	Gln	Glu	Arg	Val	Asn	Cys	Phe	
				260					265					270			
	Cys	Leu	Val	Phe	Pro	Phe	Arg	Thr	Phe	Tyr	Leu	Cys	Ala	Lys	Thr	Gly	
			275					280					285				
55	Val	Glu	Ala	Asp	Glu	Trp	Ile	Lys	Ile	Leu	Arg	Trp	Lys	Leu	Ser	Gln	
		290					295					300					
60	Ile	Arg	Lys	Gln	Leu	Asn	Gln	Gly	Glu	Ala	Arg	Ser	Asp	Leu	Gly	Arg	
	305					310					315					320	
	Ser	Ser	Leu	Asn	Arg	Ser	Phe	Leu	Pro	Arg	Asn	Ala	Leu	Ala	Gln	Glu	
					325					330					335		

Gln Val Glu Cys Phe Pro Xaa Arg Cys Asp Leu Xaa Gln Leu Gln Met
340 345

5 Lys Thr Asp Xaa Asp Phe Leu Ser Lys Thr Asn Gln Asn Arg Cys Xaa
355 360 365

Leu Gly Pro Ile Tyr His Val Ala Asp Ser Leu Cys Cys Pro Ser Xaa
370 375 380

10 Met Leu Pro Xaa Pro Xaa Glu His Xaa Ser Asn His His Xaa Asp Arg
385 390 395 400

Lys Cys Leu Asn His His Ser Xaa Val Cys Ser Leu Leu Glu His Thr
405 410 415

15 Met Glu Glu Glu Gly Phe Leu Phe Ser Leu Ile Val Val Pro Lys Pro
420 425 430

20 Ile Asp Thr Ser Cys Leu Glu Ser His Cys Glu Ser Trp Ser Ala Cys
435 440 445

Leu Thr Xaa Arg Leu Cys Tyr Xaa Pro Arg Arg Lys Gln Ile Leu Gly
450 455 460

25 Gly Leu Asp Asp Xaa Cys Arg Ile Tyr Ile Gln Ile Glu Asn Ile Lys
465 470 475 480

Tyr Phe Gln Gly Arg Gly Phe Phe Phe Xaa Phe Phe Pro Leu Tyr Thr
485 490 495

30 Lys Lys Lys Lys Lys Lys Leu Glu Gly Gly Pro Tyr Pro Xaa
500 505 510

(2) INFORMATION FOR SEQ ID NO:24:

35 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2093 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
40 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

50 TAAGGTCCAC GTCGCTCCG AGCCATCACT ACAGKMCCGC GCCGTGGCCT CTGGGCCCA 60
CAAWCTCCGR GGAGACCTGC ATCAAGATGG AGGTGAGAGT CAAGGCCTTG GTTCACTCTT 120
CCAGCCCGAG TCCAGCCCTG AATGGCGTCC GGAAGGATTT CCACGACCTC CAGTCTGAGA 180
55 CCACGTGCCA GGAGCAAGCC AATTCACTGA AGAGCTCGGC TTCTCATAAT GGAGACCTGC 240
ATCTTCACCT GGATGAACAT GTGCCTGTG TTATTGGACT TATGCCTCAG GACTACATTC 300
AGTATACTGT GCCTTTAGAT GAGGGGATGT ATCCTTTGGA AGGATCACGG AGCTATTGTC 360
60 TGGACAGCTC TTCTCCCATG GAAGTCTCTG CGGTTCCCTC TCAAGTGGGA GGGCGCGCTT 420
TCCCCGAGGA TGAGAGTCAG GTAGACCAGG ACCTAGTTGT CGCCCCAGAG ATCTTCGTGG 480

ATCAGTCCGT GAATGGCTTG TTGATTGGCA CCACGGGAGT CATGTTGCAG AGCCCCGAGAG 540
 CGGGTCACGA TGATGTCCTC CCACTCTCAC CATTGTACCC TCCAATGCAG AATAATCAAA 600
 5 TCCAAAGGAA CTTCAGTGA CTCACCTGCA CAGAAGCCCA CGTGGCTGAA AGTATCGCT 660
 GTCATTGTAA TTTTGTATCC AACTCTGTCT CTGGGGTTGC AAGAGTTTAT GACTCAGTGC 720
 10 AAGTAGTGG TCCCATGGTT GTGACAAGCC TTACAGAGGA GCTGAAAAAA CTTGCAAAAGC 780
 AAGGATGGTA CTGGGGACCA ATCACACGTT GGGAGGCGA AGGGAAGCTA GCAAAACGTC 840
 CAGATGGTTC TTTTCTTGTG CCGGACAGTT CTGACGACCG TTACCTTTTA AGCTTTAGCT 900
 15 TTGCTCTCCA TGGTAAACA CTTCACACTA GAATTGAGCA CTCAAATGGT AGGTTTAGCT 960
 TTTATGAACA GCCAGATGTG GAAAGGACAT ACTCCATAGT TGATCTAATT GAGCATTCCTA 1020
 TCCAGGGACT CGAAAATGGA GCTTTTGTGT ATTCAAGGTC TCGGCTGCCT GGATCTGCAA 1080
 20 CTTACCCCGT CAGACTGACC AACCCAGTGT CCCGGTTCAT GCAGGTGCGC TCGTTGCACT 1140
 ACCTGTGTCT TTTTGTGATA CGTCAGTATA CCAGAATAGA CTTAATTTCAG AAATGCCCTT 1200
 25 TGCCAAACAA AATGAAGGAT TATTTACAGG AGAAGCACTA CTGAAAGATT GAGAACCCCTG 1260
 CATCTTGCAC TTTGGGAATA AGAACAAGAG ATTGAAATAC AGTTTACAAA CTTTCATTGC 1320
 CATCAAAATC TTTTGTCTGC ATAATATTT CAGTTTATG TGTAAGAGAG TCATCAGTTT 1380
 30 GTTTAGGGGT GGGGAAGTGT CAGCAAGGTG TCTTGGGTTT ATTTTGGTTC TTTAAAAAG 1440
 GGAAGTCTTG AAGTTTGTGA RGTGTTGAAT TATGTTTCAT CAATGTGCAG AATAATCACA 1500
 35 ATGTGAATTA TCAAAATCTC CTCATGCCC CCCCCGCCA KTCCTTTGCT GCTATCCACT 1560
 GTGATTTTTA TGCATTAATA GCMCATTCA TGTKTTTCA ACCCTAAGTA AAGTTGAATG 1620
 AAACCTAACR GAATGGAAT TGTATTTCT TTTAAATGG YCCATTTCC AAAAMARGTG 1680
 40 TGAATAAMC AWMCTGTGKT GAATAAAACM MGRAWTWMM WWTARCA MYG BAGRTGRGTT 1740
 TTTAATCTYY TAMYTTDAAA AGATTTATTT AGAATYKKA ATTGACMTAA TATTTGGTWA 1800
 45 TBGGRMCGGR GATCTGSAAC ATATKYTTTA ACAACAWTTT WTKKCYTTA ATKKDTTTY 1860
 AARGKTGGCB TTATTWHTTT GGBKBSVAA AGKWBVAHTT CTCYGYTSCC YTCGTTTCA 1920
 TCTTCTAGTT TGTGNIATTT TAATAAATGG CCTTACATTA AAAAATGTGA AAGAAATGTA 1980
 50 TACCACCAAT TTAGAAATTG TTGCCTTTTC TGTAAATAAA CTCGGGTACA AATNGSCATA 2040
 ACATGAAAC CTATGGAAC AGAATTATTA TTAAAGAAAT ATTAGATGAT CAT 2093

55 (2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1748 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

60

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

5	ATGGAGGCCG GAGAGGAACC GCTGCTGCTG GCCGAACTCA AGCCCGGGCG CCCCCACCAG	60
	TTTGATTGGA AGTCACGCTG TGA AACCTTG AGCGTGGCCT TC TCGCCAGA CGGTTCTCTG	120
10	TTCCGCTGGT CTCAGGACA CTGCGTGGTC AAGCTGGTCC CTTGGCCCTT AGAGGAACAG	180
	TTTCATCCCTA AAGGATTCGA AGCCAAGAGC CGAAGCAGCA AGAATGACCC AAAAGGACGG	240
15	GGCAGTCTGA AGGAGAAGAC GCTGGACTGT GGCAGATTG TGTGGGGGCT GGCCTTCAGC	300
	CCATGGCCCT CTTCAACCAG CAGGAAACTC TGGGCACGTC ACCATCCCCA GGCCTTCAGT	360
	GTTTCTTGCC TGATCTGGC CACAGGTCTC AACGATGGC AGATCAAGAT TTGGGAGGTA	420
20	CAGACAGGCC TCCTGCTTCT GAATCTTTCT GGCCACCAAG ACCTCGTGAG AGATCTGAGC	480
	TTACAGCCCA CGGCGAGTTT GATTTTGGTC TCTGCATCCC GGGATAAGAC ACTTCGAATT	540
	TGGGACCTGA ATAAGCAGCG TAAGCAGATC CAGGTGTTAT CCGGCCATCT CGATCGGTT	600
25	TACTGTCTGT CCATCTCCCC TGACTGTAGC ATGCTGTGCT CTGCAGCTGG GGAGAAGTCG	660
	GTCTTTCTGT GGAGCATGCG GTCTCTACACA CTAATCCGGA AACTAGAAGG CCACCAAAAGC	720
30	AGTGTGTCTT CCTGTGATT CTCTCTGAT TCAGCCTTGC TTGTCACAGC TTCGTATGAC	780
	ACCAGTGTGA TTATGTGGGA CCCCTACACC GGCAGAGGCG TGAGGTCACT TCATCACACA	840
35	CAGCTTGAAC CCACCATGGA TGACAGTGAC GTCCACATGA GCTCCCTGAG GTCCCTGTGC	900
	TTCTCACCTG AAGGCTTGTA TCTCGCTACG GTGGCAGATG ACAGRCTGCT CAGGATCTGG	960
	GCTCTGGAAC TGAAAGCTCC GGTGCGCTTT GCTCCGATGA CCAATGGTCT TTGCTGCACA	1020
40	TTTTTYCCAC AYGGTGGAAT YATTGCCACA GGGACAAGAG ATGGCCACGT CCAGTCTCTG	1080
	ACAGCTCCTA GGGTCTGTCT CCACTTGAAG CACTTATGCC GGAAAGCCCT TCGAAGTTTC	1140
45	CTAACAACTT ACCAAGTCTT AGCACTGCCA ATCCCCAAGA AAATGAAAGA GTTCCTCACA	1200
	TACAGGACTT TTTAAGCAAC ACCACATCTT GTGCTTCTTT GTAGCAGGGT AAATGTCCT	1260
	GTCAAAGGGA GTTGCTGGA TAATGGGCCA AACATCTGGT CTTGCATTGA AATGACATTT	1320
50	CTTTGGGATT GTGAATAGAA TGTAGCAAAA CCAGATTCCA GTGTACTAGT CATGGRTCTT	1380
	TCCTCTCCCTG GGCATGTGGA AAGTCAGTCT TAGGAGGGGA GGAGATTCCA CTTGKACCG	1440
55	GCAACAGAGC CYTTACGTTT AAATTTTCA GTCCAGTTAT KGAACAGCAA GTGPTTGAAM	1500
	TCTTTCTGGY TGTGTTTGA WTTCAAAGTG GCAGTTACTG RWKGTGTGTT TTGGAATTAT	1560
	GGCAACYAAG TTAGGGCCCT CAGNGGTNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN	1620
60	NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN HNABNVNRNN NRTNNNNRMA TNNNNNNNNN	1680
	NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN	1740
	NNNNNNNN	1748

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 2198 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: cDNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

	GGCGGTGGTG ATGGCGGCAG GCGCTCGGAC AGCTCCGCTT GAGCTGAGCT CGGAGAGATC	60
20	CGTCCAGAAA GTGCCAGAA GAAACTTCCT CTTAGAAAAA CTGAAAAACAC AATATTTTATA	120
	ACACTGGAAA TTGTAAAGAA TTTGTTTAAA ATGGCTGAAA ACAATAGTAA AAATGTAGAT	180
	GTACGGCCTA AAACAAGTCG GAGTCGAAGT GCTGACAGGA AGGATGGTTA TGTGTGGAGT	240
25	GGAAAGAAGT TGTCTTGGTC CAAAAAGAGT GAGAGTTGTT CTGAATCTGA AGCCAAGAAA	300
	GGGCAGCTTA GCTGTCCTGC CATTGAGTTG GACTTAGATC ATTCTGTGG GCATAGATTT	360
30	TTAGGCCGAT CCCTTAAACA GAAACTGCAA GATGCGGTGG GGCAGTGTTT TCCAATAAAG	420
	AATTGTAGTG GCCGACACTC TCCAGGGCTT CCATCTAAAA GAAAGATTCA TATCAGTGAA	480
	CTCATGTTAG ATAMGTGYSC YTTCCACCTT CGCTCAGATT TAGCCTTTAG GTGGCATTTT	540
35	ATTAAACGAC ACACTGTTCC TATGAGTCCC AACTCAGATG AATGGGTGAG TGCAGACCTG	600
	TCTGAGAGGA AACTGAGAGA TGCTCAGCTG AAACGAAGAA ACACAGAAGA TGACATACCC	660
40	TGTTTCTCAC ATACCAATGG CCAGCCTTGT GTCATAACTG CCAACAGTGC TCTCGTTACA	720
	GGTGGTCACA TAACATGGTTC TATGATGAAC TTGATCACA ACAACAGCAT AGAAGACAGT	780
	GACATGGATT CAGAGGATGA AATTATAACG CTGTGCACAA GCTCCAGAAA AAGGAATAAG	840
45	CCCAGGTGGG AAATGGAAGA GGAGATCCTG CAGTTGGAGG CACCTCCTAA GTTCCACACC	900
	CAGATCGACT ACGTCCACTG CCTTGTTCCT GACCTCCTTC AGATCAGTAA CAATCCGTGC	960
50	TACTGGGGTG TCATGGACAA ATATGCAGCC GAAGCTCTGC TGAAGGAAA GCCAGAGGGC	1020
	ACCTTTTTC TTCGAGATTC AGCGCAGGAA GATTATTAT TCTCTGTTAG TTTTAGACGC	1080
	TACAGTCGTT CTCTTCATGC TAGAATTGAG CAGTGAATC ATAACTTTAG CTTTATGATCC	1140
55	CATGATCCTT GTGCTTCCCA TTCTCTGAT ATTACTGGGC TCCTGGAACA CTATAAGGAC	1200
	CCCAGTGCCT GTATGTTCTT TGAGCGCTC TTGTCCACTC CCTTAATCCG GAGCTTCCCC	1260
60	TTTTCCTTGC AGCATATTTG CAGAACGGTT ATTTGTAATT GTACGACTTA CGATGGCATC	1320
	GATGCCCTTC CCATTCCTTC GCCTATGAAA TTGTATCTGA AGGAATACCA TTATAAATCA	1380
	AAAGTTAGGT TACTCAGGAT TGATGTGCCA GAGCAGCAGT GATGCGGAGA GGTAGAATG	1440

	TCKACCGGAG	CTTTYGTTCC	CTTTAGTGAG	GGTTAATTTC	GAGCTTGGCG	TAATCATGGT	1500
	CATAGCTGTT	TCCTGTGTGA	AATYGTATC	CGCTCACAAT	TCCACACAAC	ATACGAGCCG	1560
5	GAAGCATAAA	GTGTAAAGCC	TGGGGTGCCT	AATGAGTGAG	CTAACTCACA	TTAATTGSGT	1620
	YGCCTCACT	GCCCGCTTTC	CAGTCGGGAA	ACCTGTCTGT	CCASCTGCAT	TAMTGAATCN	1680
10	GCCAACKGCG	NGGGANAGCG	GTNCGNTAT	TGGGCGCTCT	TCACCTTCNTC	GCTCACTGAN	1740
	TCNCTNCCCT	GGTCNNTCGN	TGCTGCTACN	GTNTCCCCCA	TCCAAGCGTT	ATACGCTATC	1800
	CNCAGAAGCT	GGAAANNNGN	AANACNNTNA	CAAAGCTCAN	TGCTANGCTA	NACGCCNTGC	1860
15	NGGCTTTTCC	TGTCCCCCCN	ACACNCTAAA	CAGCCCTCGA	GTGCAACCCN	GATATANATN	1920
	TCTTCCCTNA	ACCCCTGCCT	CTGTCCNCCG	CTNCGACTTC	GCTTCCNMG	ATTGCTTTTCN	1980
20	CCCCGTAGTC	NGTCNTAGTG	NGCNGCGCCT	TCCACCCCTC	NACCNTACG	TAMNNNNANN	2040
	CNCAAAANCC	NCCNCCCTC	NGATAAAAG	TNAGNGCCTT	NANNNCCNNG	ATAAAAAATGG	2100
	TCCCNCTACT	TCCAATGTCT	NCCNCCCGCG	TNNTCTNGCC	ACCCAANTNA	NNTTTCCGGN	2160
25	ACTGNATCCG	GTGCTANCNT	CCTGTTTCTC	CTCCCNCC			2198

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2254 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

40	CTCGGGCCCG	GATGGATCCG	CGGGAAGAG	GAAGACAAGC	GGAGCGTTGA	GCCCTTGC	60
45	ACGGTGCCCC	GCGCGTAGTG	GGAGCTTACT	CGCAGTAGCT	CTCGCTCTTC	TAATCAATGG	120
	ATAAAGTGGG	GAAATGTGG	AACAACCTAA	AATACAGATG	CCAGAATCTC	TTCAGCCACG	180
	AGGGAGGAAG	CCGTAAATGAG	AACGTGGAGA	TGAACCCCAA	CAGATGTCCG	TCTGTCAAAG	240
50	AGAAAGCAT	CAGTCTGGGA	GAGGCAGCTC	CCCAGCAAGA	GAGCAGTCCC	TTAAGAGAAA	300
	ATGTTGCCCT	ACAGCTGGGA	CTGAGCCCTT	CCAAGACCTT	TTCCAGGCGG	AACCAAAACT	360
55	GTGCCGAGA	GATCCCTCAA	GTGGTTGAAA	TCAGCATCGA	GAAAGACAGT	GACTCGGGTG	420
	CCACCCACAG	AACGAGGCTT	GCACGGAGAG	ACTCCTACTC	GCGGCACGCG	CCGTGGGGAG	480
	GAAAGAAGAA	ACATTCCTGT	TCCACAAAGA	CCCAGAGTTC	ATTGGATACC	GAGAAAAAGT	540
60	TTGGTAGAAC	TCGAAGCGCG	CTTCAGAGGC	GAGAGCGCGG	CTATGGAGTC	AGCTCCATGC	600
	AGGACATGGA	CAGCGTTTCT	AGCCGCGCGG	TCGGGAGCCG	CTCCCTGAGG	CAGAGGCTCC	660
	AGGACACGGT	GGGTTTGTGT	TTTCCCATGA	GAACCTTACG	CAAGCAGTCA	AAGCCACTCT	720

5 TTTCCAATAA AAGAAAAATM CATCTYTCGT AATTAATGCT KGAGAAATGC CCTTTCCCTG 780
 CTGGCTCRGA TTTAGCMCA AAGTGGCATT TGATTAAACA GCATACAGCT CCTGTGAGCC 840
 CACATTCAAC ATTTTTTGAT ACRTTTGATC CATCTTTGGT TTCTACAGAA GATGAAGAAG 900
 ATAGGCTTAG AGAGAGAAG CGGCTTAGTA TTGAAGAAGG GGTGATCCC CCTCCAATG 960
 10 CACAAATACA TACATTGAA GCTACTGCAC AGGTTAATCC ATTATTTAAA CTGGGACCAA 1020
 AATTAGCTCC TGAATGACT GAAATAAGTG GGGACAGTTC TGCAATTCCA CAAGCTAATT 1080
 15 GTGACTCGGA AGAGATACA ACCACCCGTG GTTTGCAGTC ACGGAGGCAG AAGCAGCGTC 1140
 AGATATCTGG AGACAGCCAT ACSCATGTTA GCAGACAGG AGCTTGGAAA GTCCACACAC 1200
 AGATTGATTA CATACTGTC CTCGTGCCCTG ATTTGCTTCA AATTACAGGG AATCCCTGTT 1260
 20 ACTGGGGAGT GATGACCCTG TATGAAGCAG AAGCCCTCTC CGAAGGGAAA CCKGAAGSCA 1320
 CGTCTTGCTC CAGGACTCT GCACAGGAGG ACTACCTCTT CTCTGTGAGT TCCGCCGCTA 1380
 25 CAACAGGATC TCTGCACGCC CGGATCGAGC AGTGGAAACA CAACTTCAGC TTGATGCCCC 1440
 ATGACCCCTG CGTGTTTCAY TCCTCCACTG TCACGGGGCT TCTCGAACAC TATAAAGAYC 1500
 CCAGTTCCTG CATGTTTTTT GAACCGTTGC TAACGATATC ACTSAATAGR ACTTTCCCTT 1560
 30 TCAGCCTGCA GTATATCTGC CGCGCAGTGA TCTGCAGATG CACTACGTAT GATGGGATTG 1620
 ACGGGCTCCC GCTACCGCTG ATGTTACAGG ATTTTTTAAA AGAGTATCAT TATAAACAAA 1680
 35 AAGTTAGAGT TCGCTGGTTG GAACGAGAAC CAGTCAAGGC AAAGTAAACT CTCGGTCCCC 1740
 CAAAGGGTGT TAACTAGGTC CGCTTTCATG TGCATCAGAC AGTACACCTA TAGCAAGCAC 1800
 ACGTAGCAGT GTTAGGCTTT TTCATACAGT ATGTAAGCTT AGTGTTAGTA TCTGTCAGAT 1860
 40 GCTACCTGCT GTTACTTATT CAGATAAACA TGGTGCCTAT TGGAAACAATA GCGGATAGAG 1920
 CTACAGGTGT TCAGTAAGAC TACAAAAACA TTTTGCTAT TTGCTAACA GTTTGGTTTT 1980
 45 TAATGGCTGT GGTATTTGAG TGAGGCAAYY CTGGGCAATT TGTATGAAG AATTCTATTT 2040
 CTTACTGAAG AACAAATWAT TAATATTGGA TGAGTATTTC AACAGTGTA CTAATGTTTG 2100
 AAATTATTTT TTCTAAGAG TTTTCCWAT AACCTCCMA AAGTCGTGAT GTTTGTAGTT 2160
 50 ACCATAATCC AGCTTTGRAG TCCMAAARGA TTAAGRCYG CCTCCCTTGT RAAAATGCCA 2220
 TTTYKGCCTC CAAGGCCTAG TGCGTCCCT NCGG 2254

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2206 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

5	GGAGCGCGGC CTGAGAGCTA ACAGCTGCTC GGAAGAGGAG CTCAGCAGCC CGGGTCGCGG	60
	AGGAGGAGGG GCGCGCCGGC TTCTGTGTGCA GCCCCAGGC CCTGAATTAC CTCGGGTGCC	120
10	CTTCCCCTGT CAGGACTTGG TCCCTCTGGG GCGCCTGAGT AGAGGGGAGC AGCAGCAGCA	180
	GCAGCAGCAG CAACCTCCCC GCGCCCCGCC TCCTCCCGGG CCCCTCCGGC CACTCGCGGG	240
	TCCTTCTCGG AAGGGCTCCT TCAAAATCCG CCTCAGTCGC CTCTTTCGCA CCAAGAGCTG	300
15	CAACGGTGGC TCCGCGCGTG GGGATGGGAC CGGCAAGAGG CCTTCTGGAG AGCTGGCTGC	360
	TTCAGCTGCG AGCCTGACAG ACATGGGAGG CTCTGCGGGC CGGAGCTGG AGCGGGGAG	420
20	GAAACCCAAG TTGACAAGAA CTCAAAGTGC CTTTCTCCG GTCTCTTCA GCCCCTGTGT	480
	CACAGGTGAA ACTGTGTGCG TTGTGGATGT GGACATTCT CAGCGGGGCC TGACCTCTCC	540
	ACACCTTCCA ACTCCCCCTC CTCTCCGAG AAGAAGCTC AGCCTCTAG ATGATATCAG	600
25	TGGGAGCTG CCTACATCTG TCCTGTGGC TCGATGGGG TCTTCTTGC AGTCTTTCCC	660
	CCTACCTCG CCTCTCCAC CCCATGCCCC AGATGCATTT CCCGGATTG CTCCTATCG	720
	AGCAGCTGAA TCCCTGCACA GCCAACCCC ACAGCACCTC CAGTGTCCCC TCTACCGGCC	780
30	TGACTCGAGC AGCTTTGAGC CAGCCTTCG AGAGTTGGAG AAGTGTGGTT GGTATTGGGG	840
	GCCAATGAAT TGGGAAGATG CAGAGTGAA GCTGAAAGG AAACCAGATG GTTCTTTCTT	900
35	GGTACGAGAC AGTTCTGATC CTGTTACAT CCTGAGCCTC AGTTTCCGAT CACAGGGTAT	960
	CACCCACCAC ACTAGAATGG AGCACTACAG AGGAACCTTC AGCCTGTGAT GTCATCCCAA	1020
40	GTTTGAGGAC CGCTGTCAAT CTGTTGTAGA GTTTATTAA AGAGCCATTA TGCATCCCAA	1080
	GAATGGAAG TTTCTCTATT TCTTAAGATC CAGGGTTCCA GGACTGCCAC CAACTCTGT	1140
	CCAGCTGCTC TATCCAGTGT CCGATTAC CAATGTCAA TCCCTCCAGC ACCTTTGCAG	1200
45	ATTCGGGATA CGACAGCTCG TCAGGATAGA TCACATCCCA GATCTCCAC TGCCTAAACC	1260
	TCTGATCTCT TATATCCGAA AGTTCTACTA CTATGATCCT CAGGAAGAGG TATACCTGTC	1320
	TCTAAAGGAA GCGCAGCTCA TTTCCAAACA GAAGCAAGAG GTGGAACCCCT CCACGTAGCG	1380
50	AGGGGCTCCC TGTGGTTCAC CACCAAGGGC ATTTGGTTGC CAAGCTCCAG CTTTGAAGAA	1440
	CCAAATTAAG CTACCATGAA AAGAAGAGGA AAAGTGAGGG AACAGGAAGG TTGGGATTCT	1500
55	CTGTGCAGAG ACTTTGGTTC CCCACGAGC CCTGGGCCTT GGAAGAAGCA CATGACCGTA	1560
	CTCTGCTGG GGTCCACCT CACACCCACC CCTGGGCATC TTAGGACTGG AGGGGCTCCT	1620
	TGGAATACTG GAAGAAGTCT CAACACTGTT TCTTTTCAA AAAAAAAAAA AAAAAAGATG	1680
60	CGGCCGCAAG CTTATTCCTT TTAGTGAGGG TTAATTTTAG CTTGGCACTG GCGCTCGTTT	1740
	TACAACGTCG TGACTGGGAA AACCTGGCG TTACCCAAC TAATCGCCTT GCAGCACATC	1800

CCCCCTTTCGC CAGCTGGCGT AATAGCGAAG AGGCCCGCAC CGATCGCCCT TCCCAACAGT 1860
 TCGCGAGCCT GAATGGCGAA TGGGACGCGC CCTGTAGCGG CGCATTAAACG CGCGCGGGT 1920
 5 GTGGTGGTTA CGCGAGCGT GACCGCTACA CTGCCAGCG CCCTACGCCC GCTCCTTTTCG 1980
 CTTTCTTCCC TTCTTTCTC GCCACGTTCC CCGCCTTCC CGTCAACTC TAAATCGGG 2040
 10 GCTCCCTTTA GGTTCGGATT TANTGCTTTA CGCACTCNAC CCAAAACTT GATTAGGTGA 2100
 TGTCACCTAT GGCACNCTG ATAAGCTTC CCCTTACTTT GATCACTTCT TTATATGATC 2160
 TTCCAATGA AACATCACCT ACTCGTCATC TTTATTTAA GATTGG 2206
 15 (2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1390 base pairs
 (B) TYPE: nucleic acid
 20 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

30 CGGACGCGTG GGTTTGGCTG TGAATATCTT ATTTGCTTGC AGTATCTGTT TCTCTTCCTA 60
 GGCTCAAGTT GGTGACCCAA GCCTATTGTA AACAAAGTAT TATCTCANNG GGAGATGCCA 120
 35 ATGGAGTAAC AATTGTGTAA CCTTACGTTT TCTGTCTGTA TATTTTTTTA AAAATCTGGT 180
 AGTTTCTGGA AAAAAAGAG AAGGGGGTTT GTAGTACTTA ACCCTATTTA TTKSCRYRWG 240
 TTTTAGTTAA TTAGTTTTTG GAATAAATGG ATTTCACTAT AGCTTTGTGG TAAATTGCA 300
 40 TTGCCTTTAT TTTATGTTTA GGCTTATTTT TAAATTAACA TTTAACAGAA ACATTTGAAA 360
 TAGAATTGTC ATGCTGCCTT TAATTAACCT AAAGACTGAT TTTAATCTGA CTATGACACT 420
 45 GAGCATATTC TTTAAATTAC TCATAATTTA TAATGCTTAA TATAATCTTA ATTTAAATTTA 480
 GCAGTTTTPAG TATAAGATGT GCCATTTTGT CCTCTGTATG TCTGAATGAA GCTATAACAT 540
 TTGCCTTTT ATTCGAGGTT TTCTTTTGA ATATGGATAA ATACACCATG ATACGGAAAC 600
 50 TAGAAGGACA TCACCATGAT GTGGTAGCTT GTGACTTTTC TCCTGATGGA GCATTACTGG 660
 CTACTGCATC TTATGATACT CGAGTATATA TCTGGGATCC ACATAATGGA GACATTCGTA 720
 55 TGGAATTTGG GCACCTGTTT CCCCCACCTA CTCCTAATTT TGCTGGAGGA GCAATGACC 780
 GGTGGGTACG ATCTGTATCT TTTAGCCATG ATGACTGCA TGTTGCAAGC CTTGCTGATG 840
 ATAAAATGGT GAGGTCTCGG AGAATTGATG AGGAATTATCC AGTGCAAGTT GCACCTTTGA 900
 60 GCAATGGTCT TTGCTGTGCC TTCTCTACTG ATGGCAGTGT TTTAGCTGCT GGGACACATG 960
 ACGGAAGTGT GTATTTTGG GCCACTCCAC GGCAGGTCCC TAGCCTGCAA CATTATGTGC 1020
 GCATGTCAAT CCGAAGAGTG ATGCCACCC AAGAAGTTCA GGAGCTGCCG ATTCCTTCCA 1080

	AGCTTTTGGG	GTTTCTCTCG	TATCGTATTT	AGAAGATTCT	GCCTTCCCTA	GTAGTAGGGA	1140
5	CTGACAGAAT	ACACTTAACA	CAAACCTCAA	GCTTTACTGA	CTTCAATTAT	CTGTTTTTAA	1200
	AGACGTAGAA	GATTTATTTA	ATTTGATATG	TTCTTGTA	GCATTTTGAT	CAGTTGARGC	1260
	TTTTAAAATA	TTATTTATAG	ACAATAGAAG	TATTTCTGAA	CATATCAAAT	ATAAAATTTT	1320
10	TTAAAGATCT	AACGTGAAA	AACATACATA	CCTGTACATA	TTTAGATATA	AGCTGCTATA	1380
	TGTTGAATGG						1390



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C12N 15/12, C07K 14/47, 16/18, C12N 15/62	A3	(11) International Publication Number: WO 99/03993 (43) International Publication Date: 28 January 1999 (28.01.99)
(21) International Application Number: PCT/US98/14544 (22) International Filing Date: 17 July 1998 (17.07.98) (30) Priority Data: 60/053,153 18 July 1997 (18.07.97) US 60/053,244 18 July 1997 (18.07.97) US 60/055,804 15 August 1997 (15.08.97) US 60/055,853 15 August 1997 (15.08.97) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventor: JOHNSON, James, A.; 205 Mary Alice Drive, Los Gatos, CA 95032 (US). (74) Agents: MCLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 3 June 1999 (03.06.99)
(54) Title: SUPPRESSORS OF CYTOKINE SIGNALING; RELATED REAGENTS (57) Abstract <p>Purified genes encoding intracellular regulatory molecules from a human, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding these molecules are provided. Methods of using said reagents and diagnostic kits are also provided.</p>		

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/14544

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C07K16/18 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. STARR ET AL: "A family of cytokine-inducible inhibitors of signalling" NATURE, vol. 387, no. 6636, 26 June 1997, pages 917-921, XP002085491 LONDON GB cited in the application see the whole document ---	1-9
A	T.A ENDO ET AL: "A new protein containing an SH2 domain that inhibits JAK kinases" NATURE, vol. 387, no. 6636, 26 June 1997, pages 921-924, XP002085492 LONDON GB cited in the application see the whole document ---	1-9
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

17 December 1998

Date of mailing of the international search report

15.04.99

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

LE CORNEC N.D.R.

INTERNATIONAL SEARCH REPORT

In: National Application No

PCT/US 98/14544

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	T. NAKA ET AL: "Structure and function of a new STAT-induced STAT inhibitor" NATURE., vol. 387, no. 6636, 26 June 1997, pages 924-929, XP002088455 LONDON GB cited in the application see the whole document ---	1-9
A	A. YOSHIMURA ET AL: "A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to Tyrosine-phosphorylated interleukin-3 and erythropoietin" EMBO JOURNAL., vol. 14, no. 12, 1995, pages 2816-2826, XP002088456 EYNHAM, OXFORD GB cited in the application see the whole document ---	1-9
P,X	WO 98 20023 A (THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH) 14 May 1998 see the whole document especially see examples 11,17,18 see page 101 - page 102 ---	1-9
P,X	M. MASUHARA ET AL: "Cloning and characterization of novel CIS family genes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS., vol. 239, October 1997, pages 439-446, XP002088457 ORLANDO, FL US see the whole document ---	1-9
T	D.J. HILTON ET AL: "Twenty proteins containing a C-terminal SOCS box form five structural classes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 95, January 1998, pages 114-119, XP002085497 WASHINGTON US see the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/14544

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 5.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Please see extra sheet, Subject 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (1-9) all partially

Human SOCS14. Production by genetic engineering. Antibody.
Fusion protein.

2. Claims: (1-9) all partially

Murine SOCS15. Production by genetic engineering. Antibody.
Fusion protein.

3. Claims: (1-9) all partially

Murine SOCS17. Production by genetic engineering. Antibody.
Fusion protein.

4. Claims: (1-9) all partially

Human SOCS18. Production by genetic engineering. Antibody.
Fusion protein.

5. Claims: (1-9) all partially

human SOCS19. Production by genetic engineering. Antibody.
Fusion protein.

6. Claims: (1-9) all partially

Murine WDS12. Production by genetic engineering. Antibody.
Fusion protein.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 98/14544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820023 A	14-05-1998	AU 4694397 A	29-05-1998